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Diencephalic amnesia. N. R. Graff-Radford, D. Tranel, G. W. Van Hoesen and J. P. Brandt

Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. K. L. Leenders, D. Perani, A. A. Lammertsma, J. D. Heather, P. Buckingham, M. J. R. Healey, J. M. Gibbs, R. J. S. Wise, J. Hatazawa, S. Herold, R. P. Beaney, D. J. Brooks, T. Spinks, C. Rhodes, R. S. J. Frackowiak and T. Jones 27

Brainstem auditory evoked potentials and somatosensory evoked potentials in pontine haemorrhage. Correlations with clinical and CT findings. A. Ferbert, H. Buchner and H. Brückmann 49

Responses of leg muscles in humans displaced while standing. Effects of types of perturbation and of postural set. A. Nardone, A. Giordano, T. Corra and M. Schieppati 65

Three-dimensional computergraphic analysis of apraxia. Neural representations of learned movement. H. Poizner, L. Mack, M. Verfaellie, L. J. Gonzalez Rothi and K. M. Heilman 85

Motor learning in patients with cerebellar dysfunction. J. N. Sanes, B. Dimitrov and M. Hallett 103

Reevaluation of the ultrastructural pathology of experimental Creutzfeldt-Jakob disease. Serial studies of the Fujisaki strain of Creutzfeldt-Jakob disease virus in mice. P. P. Liberski, R. Yanagihara, D. M. Asher, C. J. Gibbs Jr and D. Carleton Gajdusek 121

Cerebellar infarction in the territory of the anterior and inferior cerebellar artery. A clinicopathological study of 20 cases. P. Amarenco and J.-J. Hauw 139

Ability to detect angular displacements of the fingers made at an imperceptibly slow speed. J. L. Taylor and D. I. McCloskey 157

Baroreceptor dysfunction in acrylamide axonal neuropathy. P. M. Satchell 167

Recovery of voluntary movement in hemiplegic patients. Correlation with degenerative shrinkage of the cerebral peduncles in CT images. T. Warabi, K. Inoue, H. Noda and S. Murakami 177

Peripersonal and vertical neglect. P. A. Shelton, D. Bowers and K. M. Heilman 191

Premotor cortex and conditional motor learning in man. U. Halsband and H.-J. Freund 207

Konzo, an epidemic upper motor neuron disease studied in Tanzania. W. P. Howlett, G. R. Brubaker, N. Mlingi and H. Rosling 223

Cerebral control of directed visual attention and orienting saccades. S. Nagel-Leiby, H. A. Buchtel and K. M. A. Welch 237

Book reviews 277

Announcements 289

71

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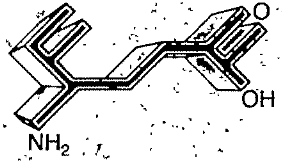

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Book reviews 277

Announcements 289

Brain (1990), **113**, 1–25

DIENCEPHALIC AMNESIA

by NEILL R. GRAFF-RADFORD,[1] DANIEL TRANEL,[1] GARY W. VAN HOESEN,[2] *and* JOAN P. BRANDT[1]

(*From the* [1]*Division of Behavioral Neurology and Cognitive Neuroscience, Department of Neurology, and the* [2]*Department of Anatomy, University of Iowa College of Medicine, Iowa City, Iowa, USA*)

SUMMARY

The anatomical basis and cognitive profile of diencephalic amnesia remain unclear. We report a two-part study. First, we studied 4 patients with bilateral medial thalamic infarctions using magnetic resonance imaging and comprehensive neuropsychological testing. All patients were followed for more than 1 year. Using a stereotactic method, we plotted the lesions in an atlas delineating the probable structure involved. Secondly, in 2 monkeys, using autoradiography, we traced the pathway from the amygdala to the dorsomedial nucleus, paying particular attention to the intrathalamic course of the amygdalothalamic projections.

Our findings were (1) patients develop amnesia when infarctions are located anteriorly; (2) in patients with amnesia, the lesions can be small and strategically located, probably interfering with both hippocampal-related neural structures such as the mamillothalamic tract, and amygdala-related neural structures such as the ventroamygdalofugal pathway; and (3) a specific component of the latter is situated lateral but immediately adjacent to the mamillothalamic tract in the monkey, enabling both structures to be damaged bilaterally by small mirror image lesions. The amnesia is characterized by deficits in anterograde verbal and visual learning and in retrograde amnesia, but motor learning is preserved. We raise the possibility that bilateral diencephalic lesions may interfere particularly with temporal aspects of memory.

INTRODUCTION

The clearest examples of chronic anterograde amnesia in animal and man occur with lesions in either the medial temporal area (Scoville and Milner, 1957; Corkin, 1984) or the diencephalon (Victor *et al.*, 1971). For the medial temporal lobe, the evidence in the monkey indicates that amnesia is worse when both the hippocampal formation or its connections and the amygdala or its connections are damaged (Mishkin, 1982). Since the hippocampal formation and the amygdala have powerful connections with the diencephalon, an important question is, are the diencephalic nuclei and/or the connections of *both* these medial temporal structures affected when amnesia occurs with diencephalic damage? While this has been suggested (Aggleton and Mishkin, 1983*b*), the answer remains unclear for many reasons. (1) The diencephalon contains many nuclei and projections in a compact space so that lesions in this area that cause amnesia often damage several nuclei and/or their connections, making it difficult to determine the responsible structures. One of the ways of sorting this out is to have control cases with diencephalic damage but without amnesia. However, only a few such patients have been reported (Kritchevsky *et al.*, 1987). (2) Reports often have either good neuropsychological

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documentation of amnesia (Mills and Swanson, 1978; Schott *et al.*, 1980; Speedie and Heilman, 1982; Goldenberg *et al.*, 1983; Guberman and Stass, 1983; Winocur *et al.*, 1984; von Cramon *et al.*, 1985; Rousseaux *et al.*, 1986; Gentilini *et al.*, 1987) or good anatomical description of the lesions based on autopsy or stereotactic plottings (Castaigne *et al.*, 1981) but only a few studies have both (Mair *et al.*, 1979; Barbizet *et al.*, 1981; Mori *et al.*, 1986). Further, in some studies, memory is only tested acutely (Dehaene, 1982; Swanson and Schmidley, 1985; Bogousslavsky *et al.*, 1986; Meissner *et al.*, 1987), and thus a chronic amnesia has not been established.

The subicular cortex, which is the principal output sector of the hippocampal formation, has powerful projections to the mamillary bodies and anterior thalamic nuclei via the fimbria-fornix. The mamillothalamic tract connects the mamillary body to the anterior thalamic nuclei. While these are classic features of neuroanatomy, the linkage between the amygdala and dorsomedial thalamic nucleus, although known to exist experimentally, is more difficult to characterize. In particular, its spatial relationship to the mamillothalamic tract is unclear, although von Cramon *et al.* (1985) have speculated that it may course in the internal medullary lamina medial to the mamillothalamic tract.

In an attempt to focus on the anatomical questions that have been raised about diencephalic amnesia, we report a two-part study. First, we studied 4 patients with bilateral thalamic infarcts, all in the interpeduncular profundus arterial territory. All patients had magnetic resonance imaging (MRI) and comprehensive neuropsychological testing in the chronic stage. Using a technique first described by Archer *et al.*, (1981) and validated in a postmortem study by Graff-Radford *et al.* (1985*a*), we localized the lesions anatomically. We then attempted to relate the patients' performance on memory tests to the location of the lesions.

Secondly, because it was important to know as accurately as possible the course of the amygdalothalamic projections, we traced this pathway in the nonhuman primate. These monkeys received tritiated amino acid injections in the basolateral nuclei of the amygdala, and the pathway from the amygdala to the dorsomedial nucleus was studied using autoradiography. Of special interest was the intrathalamic course of this pathway relative to the mamillothalamic tract, that is, could both these pathways be damaged by small strategically located mirror image lesions?

Another important issue is the pattern of amnesia in patients with diencephalic infarcts. It has clearly been established that patients with medial thalamic infarcts may develop an anterograde verbal and visual amnesia (Winocur *et al.*, 1984; Graff-Radford *et al.*, 1985*b*; von Cramon *et al.*, 1985; Rousseaux *et al.*, 1986; Gentilini *et al.*, 1987). What is little explored is the pattern of retrograde amnesia and these patients' performance on motor learning tasks. In this paper we will attempt to address these issues and discuss the implications of our findings in relation to the possible role of the diencephalon in memory.

CASE REPORTS

Case 1

A 68-yr-old right-handed retired teacher was in excellent health until June 20, 1982 when she was suddenly found to be confused. She was admitted to hospital obtunded and remained somnolent for the first 10 days.

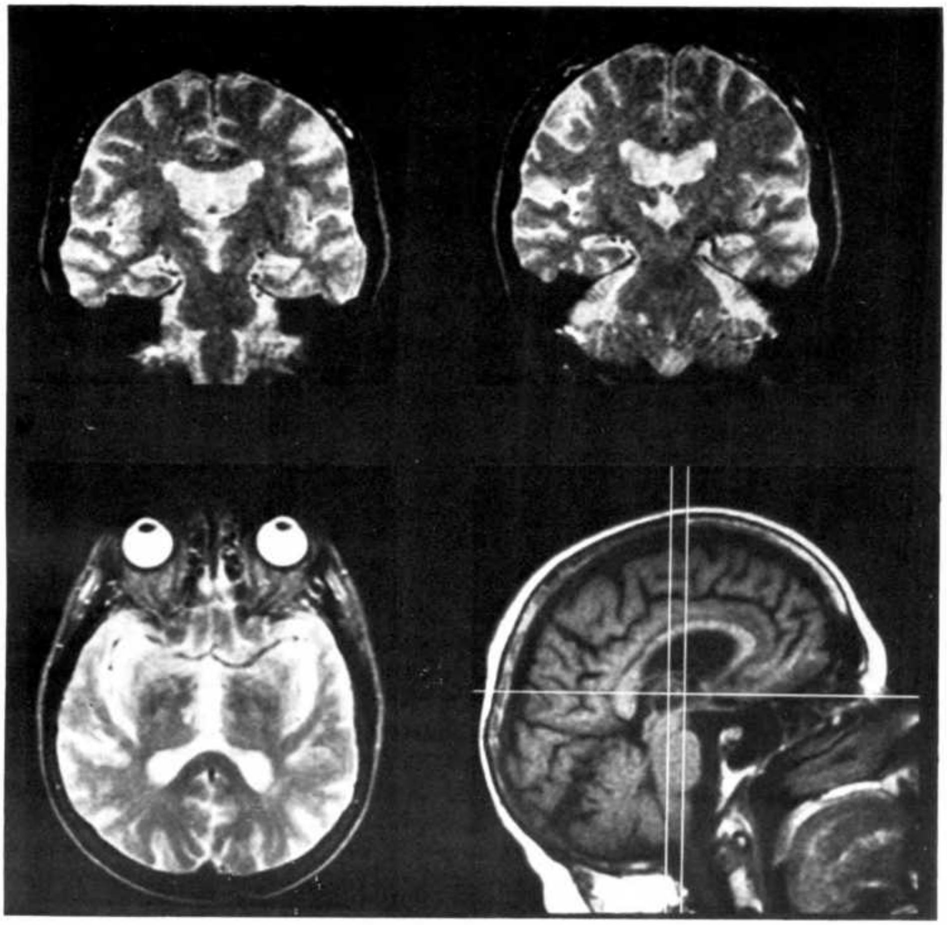

FIG. 1. Lesions in *Case 1* shown on both axial and coronal slices. The location of these slices is drawn on the midsagittal slice.

There was a past history of borderline diabetes, but no history of hypertension or smoking. Examination revealed a supranuclear vertical gaze paresis. A CT scan 10 days after admission showed bilateral enhancing medial thalamic infarctions.

The patient was discharged and lived in her own home with permanent live-in help because of a significant memory impairment. The family noted a personality change in that she was less inhibited. Over the next 5 yrs she was seen several times in the neurology clinic and underwent neuropsychological testing. Her memory deficits remained stable.

On September 25, 1987 she underwent MRI which confirmed the bilateral thalamic infarcts and no other lesions (fig. 1). She also had neuropsychological testing which revealed a stable pattern of amnesia.

Case 2

A 19-yr-old left-handed woman had the sudden onset of confusion in April 1986 and was admitted to the University of Iowa Hospitals. She had no previous illness but was on contraceptive pills. She was intermittently drowsy, had right emotional facial weakness, mild drift of the right arm, and normal sensation

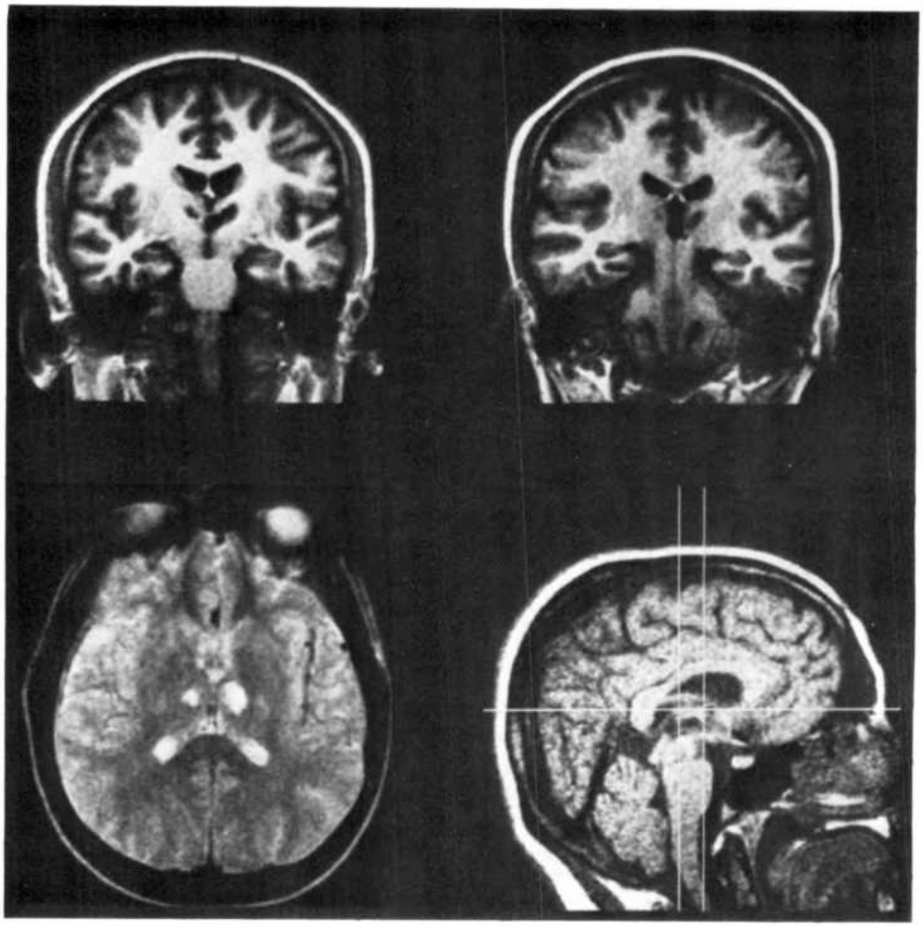

FIG. 2. Lesions in *Case 2* shown on both axial and coronal slices. The location of these slices is drawn on the midsagittal slice.

and reflexes. She remained confused and drowsy for the first week in hospital. CT showed bilateral medial thalamic infarctions. Echocardiography and arteriography were normal. MRI in October 1986 revealed bilateral thalamic infarcts without other lesions (fig. 2).

Over the next year she underwent neuropsychological evaluation three times, the last time in July 1987. Since her stroke her family have noticed that she is socially uninhibited and laughs inappropriately. Examination in July 1987 showed full eye movements, a decreased right nasolabial fold, and decreased swing of the right arm while walking. The patient's family noted that she had to be reminded many times to complete certain tasks.

Case 3

At the end of January 1987 a 57-yr-old right-handed farmer was found by his wife to be snoring and was difficult to arouse. For 2 h she tried to wake him and then called the ambulance. He awoke briefly some hours later in hospital but became somnolent again and remained so for several days. Two weeks later he was transferred to the University of Iowa Hospitals. There was no history of hypertension, diabetes,

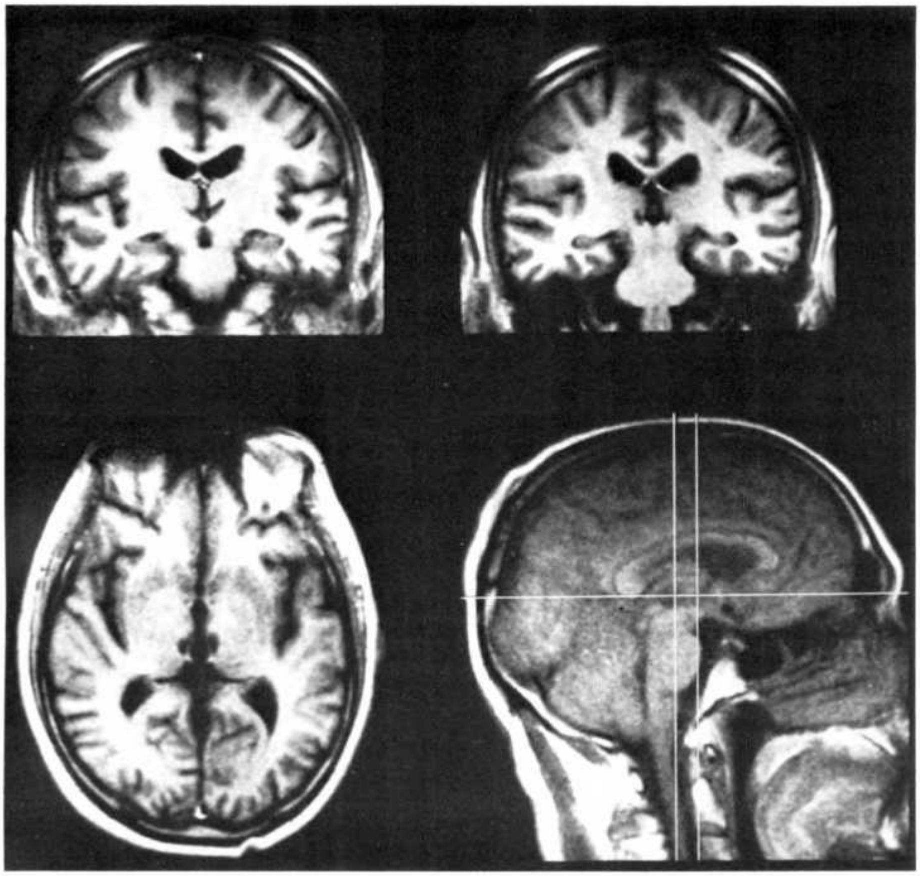

FIG. 3. Lesions in *Case 3* shown on both axial and coronal slices. The location of these slices is drawn on the midsagittal slice.

smoking, or alcohol abuse. Except for increased somnolence neurological examination was normal. MRI revealed bilateral medial thalamic infarctions (fig. 3). Echocardiography showed an atrial myxoma. Cerebral angiography was normal.

The patient underwent cardiac surgery and the atrial myxoma was successfully removed. He was seen in the neurology clinic in May and October 1987 and March 1988, and underwent neuropsychological evaluation and a repeat MRI of the head. The patient has returned to farming and he and his family deny any memory deficit.

Case 4

A 56-yr-old right-handed factory worker had a sudden onset of unresponsiveness, lasting 2 h, on February 5, 1987. He was taken to the local hospital, regained consciousness, and no focal neurological deficits were found. He had no history of hypertension, diabetes, smoking, or cardiac disease. There was a past history of bladder cancer resected in 1980 without recurrence. CT, EEG, ECG and cerebral angiography were normal. MRI showed a small left occipital and bilateral thalamic infarctions (fig. 4). On referral to the neurology clinic at the University of Iowa on March 4, 1987 he was found to have down and upbeat

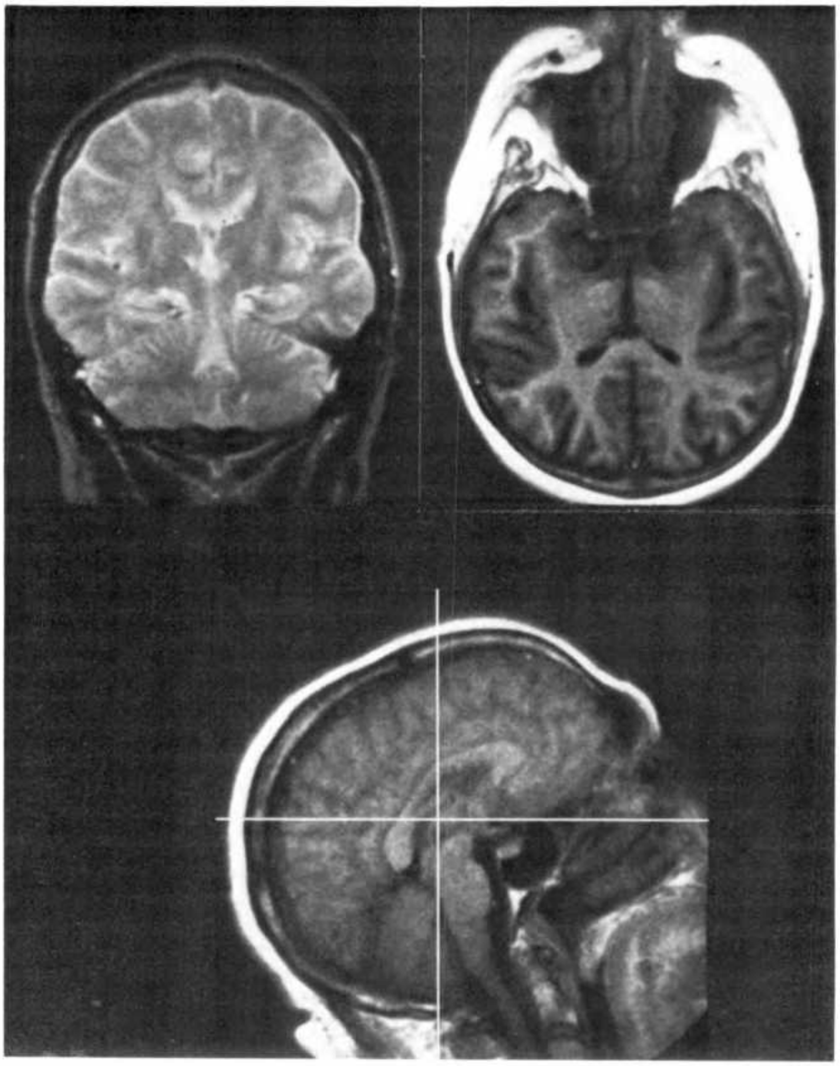

FIG. 4. Lesions in *Case 4* shown on both axial and coronal slices. The location of these slices is drawn on the midsagittal slice.

nystagmus and mild pronator drift on the right. He returned in May 1987 and March 1988, and underwent neuropsychological testing. Repeat MRI was performed in May 1987. The patient has returned to his usual activities and he and his family note no memory deficit.

METHODS

Neuroradiological study

All 4 patients underwent MRI in the chronic stage of the disease, coincident with neuropsychological testing. The scanner was a Picker International Superconducter with an 0.5 Tesla magnet. Images were obtained in sagittal, axial and coronal planes using both T1 and T2 weighted imaging methods. We have previously described in detail the method of localizing the lesions (Kritchevsky *et al.*, 1987). Archer *et al.* (1981) originally described this method using CT and we confirmed its accuracy in a postmortem study (Graff-Radford *et al.*, 1985*a*). The method is based on the Schaltenbrand and Wahren Atlas (1977) and the rationale is to find the 3-dimensional location of the lesion in relation to the anteroposterior commissure line (AP line), i.e., how far is the lesion (1) ahead of or behind the commissures; (2) above or below the AP line; and (3) lateral to the midline.

In essence, the anterior and posterior commissures are identified on the midsagittal slice. (The anterior commissure is located below the juncture of the fornix and corpus callosum while the posterior commissure can be localized at the point where the cerebral aqueduct forms.) The anterior commissure/posterior commissure line (AC/PC line) is drawn between the commissures. Next, lines marking the centres of the horizontal and coronal slices containing the lesion are superimposed by the computer on this midsaggital slice and from where these lines intersect, a line perpendicular to the AC/PC line is drawn. Measuring the distance from the anterior commissure to where the perpendicular line intersects the AC/PC line gives the distance of the centre of the coronal slice to the anterior commissure. The distance above or below the AP line of the centre of the axial slice is obtained by measuring the perpendicular height above or below the AP line of intersection of the centres of the coronal and axial slices. The medial/lateral dimension of the lesion is measured on both the axial and coronal slices and the distances from the centre of the third ventricle to the most medial centre, and most lateral part of the lesion are noted. At these 3 distances the dimensions of the lesions are measured anterior/posterior in the axial slice(s) and superior/inferior on the coronal slice(s). The lesion is then plotted on the three sagittal plates in the Schaltenbrand and Wahren Atlas corresponding to the medial, middle, and lateral distances of the lesion from the midline. Note that the AP diameter is plotted in the same plane as the axial slice and the superior/inferior diameter the same plane as the coronal slice. The planes of the axial and coronal slices in relation to the AP line are obtained by measuring the angles these slices make when they intersect the AP line on the midsagittal view. In all instances the magnification factor of the MRI and magnification of the Atlas are taken into account. A way to check the accuracy of the above method is to take advantage of the fact that the MRI image is plotted on a grid system such that the location of anterior/posterior limits of the lesion on the axial slice, and the superior/inferior limits of the lesions on the coronal slice, can be transferred to the midsagittal slice on the anteroposterior and superoinferior grids, respectively. On the midsagittal slice, perpendicular lines are dropped from the top grid delineating the anteroposterior limits of the lesion and horizontal lines are drawn from the posterior grid delineating the superior/inferior limits of the lesion. The lesion is located where the perpendicular and horizontal lines intersect. This location in relation to the AP line can be measured and plotted in the Atlas.

Anatomical study

The basolateral nuclei of the amygdala in 2 monkeys were injected with tritiated amino acids and autoradiography was used to detect the anterograde axoplasmic transport.

TABLE 1. NEUROPSYCHOLOGICAL TESTS

Orientation	Temporal Orientation Test[1]
Intelligence	Wechsler Adult Intelligence Scale-R[2]
Language	Multilingual[3] and Boston Diagnostic Aphasia Examination[4] (selected subtests)
Visuospatial abilities	Copy of the Rey-Osterreith Complex Figure[5]
	Facial Discrimination Test[1]
	Judgement of Line Orientation Test[1]
Executive control	Wisconsin Card Sorting Test[6]
	Controlled Oral Word Association Test[3]

[1]Benton *et al.* (1983). [2]Wechsler (1981). [3]Benton (1976). [4]Goodglass and Kaplan (1983). [5]Lezak (1983). [6]Heaton (1981).

TABLE 2. MEMORY TESTS

Verbal memory	Rey Auditory Verbal Learning Test with 30 min delayed recall and recognition[1]
	Wechsler Memory Scale (subtests logical memory, paired associates) and 30 min delayed recall[2]
	Craik Tulving Encoding[3]
	Release from proactive interference[4]
	Warrington Recognition Memory Test (words)[5]
Visual memory	Benton Visual Retention Test[6]
	Rey-Osterreith Figure Recall (30 min delay)[7]
	Warrington Recognition Memory Test (faces)[8]
Retrograde memory	Autobiographical construction and interview
	Recall of US Presidents
	Boston Famous Faces Test[9]
	Boston Recognition of Events Test[9]
	Boston Recall of Events Test[9]
	Squire Recall and Recognition of Past Events[10] (Forms A and B)
Motor learning	Rotor Pursuit Learning (1 h delayed recall)[11]
	Mirror Tracing (1 h delayed recall)[12]

[1] Lezak (1983), p. 422. [2] Wechsler (1945). [3] Craik and Tulving (1975). [4] Wickens (1970). [5] Warrington (1984). [6] Benton (1974). [7] Lezak (1983), p. 395. [8] Warrington (1984). [9] Albert *et al.* (1979). [10] Squire *et al.* (1989). [11] Corkin (1968); Eslinger and Damasio (1986). [12] Milner (1962).

Neuropsychological study

The first 3 patients were tested in the first month after onset and all 4 patients were tested in the chronic stage. In the chronic stage Case 1 was tested several times, finally 6 yrs after the stroke; Case 2 more than 1 yr after her stroke; Case 3 6 and 12 months after his stroke; and Case 4 3 and 12 months poststroke.

The neuropsychological examination probed the following: orientation, intellect, speech and language, visuospatial and visuoperceptual processing, 'executive control', and memory. With regard to memory, the following functions were tested: anterograde verbal, anterograde visual, retrograde memory and motor learning. A complete list of the neuropsychological tests is given in Tables 1 and 2.

RESULTS

Neuroradiological study

Axial and coronal slices showing the lesions, together with the centre of these slices drawn on the midsagittal view, are shown in figs 1–4. Fig. 5A (left side) and B (right side) show the results of plotting the lesions on the sagittal sections in the Atlas 5.15 mm from the centre of the third ventricle (Plate 39 in the Schaltenbrand and Wahren Atlas). The lesions in Cases 1 and 2 are situated more anteriorly and involve the mamillothalamic tract, and the pathway from the inferior thalamic peduncle to the dorsomedial nucleus. The latter is true on both sides for Case 1 and on the left for Case 2. Case 2 also has involvement of the anterior nuclei bilaterally. In Case 3 there are large lesions affecting mainly the dorsomedial nuclei bilaterally. Case 4 has small bilateral lesions in the lower part of the dorsomedial nuclei. In both Cases 3 and 4 the mamillothalamic tract is spared. Cases 1–3 involve the midline nuclei bilaterally.

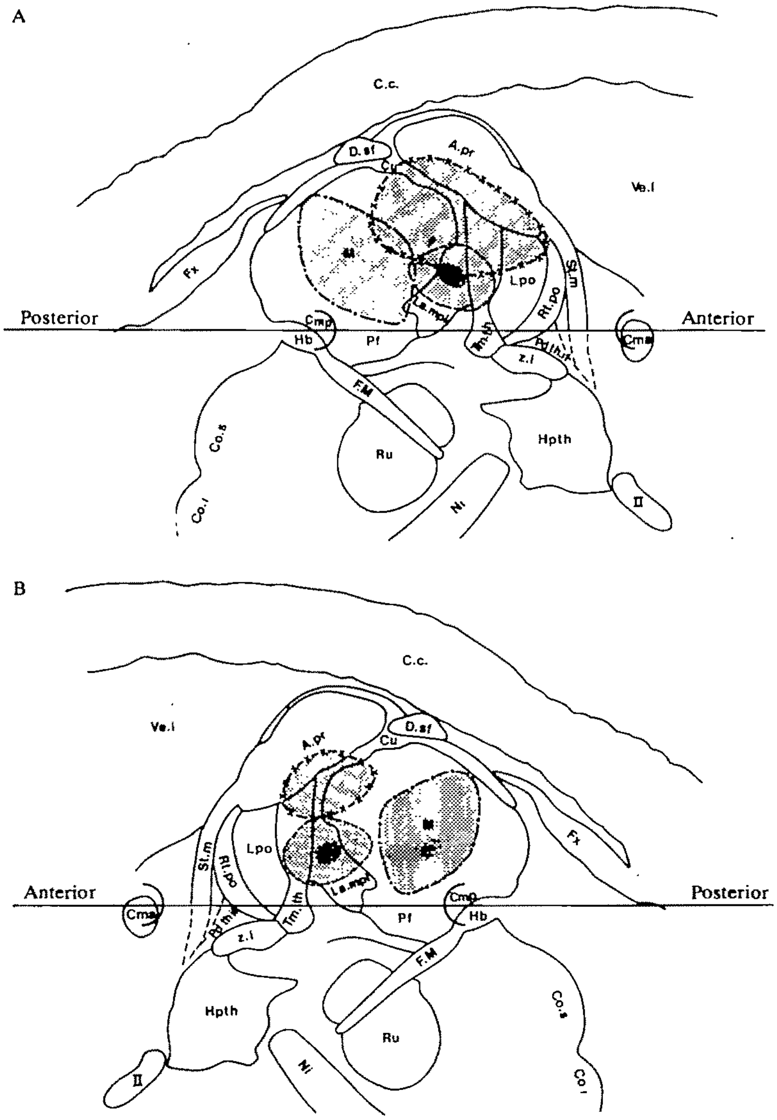

FIG. 5. A, left-sided lesions, B, right-sided lesions on the sagittal plates 5.5 mm from the midline in the Schaltenbrand and Wahren Atlas. The lesion in *Case 1* is small but strategically located, probably damaging the mamillothalamic tract (Tm.th) and interrupting fibres from the inferior thalamic peduncle (Pd thif). In *Case 2* the lesion also damaged the mamillothalamic tract. In addition, the anterior nuclei are damaged. Fibres from the inferior thalamic peduncle are probably only partly interrupted as they head for the superior part of the dorsomedial nuclei. The anterior part of the dorsomedial nuclei is damaged. In *Case 3* the dorsomedial nuclei are damaged bilaterally but the mamillothalamic tract is preserved. The lesions in *Case 4* may have partially interrupted fibres coming from the inferior thalamic peduncle but the mamillothalamic tract probably was spared. Case 1 (— — —); Case 2 (–x–x); Case 3 (– · –); Case 4 (· · · ·).

Abbreviations: A.pr = anterior nuclei; C.c. = corpus callosum; Co.i = inferior colliculus; Co.s = superior colliculus; Cma = anterior commissure; Cmp = posterior commissure; D.sf = lateral dorsal nucleus; F.m = fasciculus retroflexus; Fx = fornix; Hpth = hypothalamus; Hb = habenula; La.mpi = lamella medialis polaris; Lpo = lateral posterior nucleus; M = dorsomedial nucleus; Ni = substantia nigra; Pd.thif = inferior thalamic peduncle; Pf = parafascicular nucleus; Rt.po = reticular nucleus; Ru = red nucleus; St.m = stria habenularis; Tm.th = mamillothalamic tract; Ve.l = lateral ventricle; z.i. = zona incerta; II = second cranial nerve.

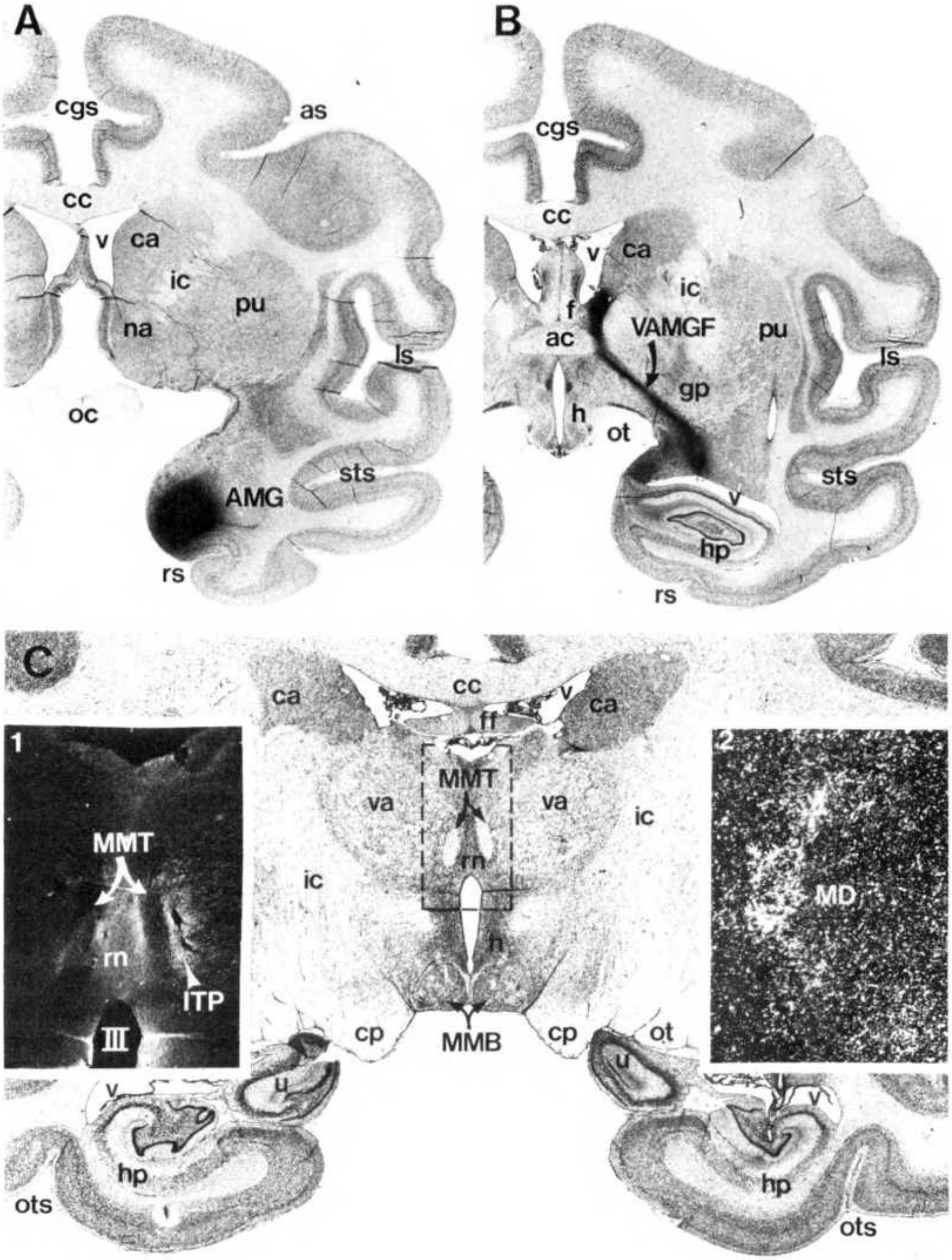
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FIG. 6.

Anatomical study

Fig. 6A shows the injection site in the amygdala from 1 case. The injection in this case labelled the accessory basal and mediobasal nuclei of the amygdala, as well as the deep layers of the adjacent entorhinal cortex. Fig. 6B and C demonstrates the course of a major component of the ventroamygdalofugal pathway that links the amygdala to various basal forebrain structures such as the bed nucleus of the stria terminalis, nucleus accumbens, and nucleus basalis of Meynert. However, a significant portion of this large neural system turns caudally in the vicinity of the ventromedial part of the globus pallidus and enters the thalamus medial to the anterior limb of the internal capsule (fig. 6C1). These axons form a part of inferior thalamic peduncle and terminate in the dorsomedial nucleus of the thalamus (fig. 6C2). In passing through the ventral anterior nucleus they assume a position immediately lateral to the mamillothalamic tract.

Neuropsychological study

Table 3 presents the overall results of the neuropsychological tests and Tables 4 and 5 give the detailed scores of the memory testing. Figs 7 and 8 show the results on the remote memory tests and motor learning tests, respectively. None of the patients had a significant global decline in intellectual functioning or was aphasic, and in all patients visuospatial abilities were normal in the chronic stage. (The IQ scores for Case 2 were in the borderline range, but were considered to be normal given the patient's educational and occupational background.) In all patients 'executive control' function (as measured by the Controlled Oral Word Association Test and the Wisconsin Card Sorting Test) was mildly to moderately impaired. In addition, by family report and clinical observation, all patients demonstrated personality changes, characterized primarily by disinhibition and lack of motivation.

Tables 4 and 5 show that Cases 1 and 2 have severe anterograde verbal and visual memory deficits; Cases 3 and 4 have milder deficits evident only on delayed tasks. Case

FIG. 6. (Opposite) A, Nissl-stained transverse section from the Rhesus monkey brain developed for autoradiography showing the location of tritiated amino acids injected into the medial parts of the basolateral amygdaloid nuclei and the deep layers of the entorhinal cortex. B, transverse section from the same animal demonstrating the ventroamygdalofugal pathway (VAMGF) in its course from the posterior amygdala beneath the globus pallidus (gp) to the bed nucleus of the stria terminalis at the base of the body of the lateral ventricle (v). C, Nissl-stained transverse section from the same case at the level of the uncus (u) and mamillary bodies (MMB). Note the midline region of the thalamus (outlined rectangle) and the position of the mamillothalamic tracts (MMT). Inset 1 is a dark-field photomicrograph of the rectangular area that demonstrates titrium-labelled axons in the inferior thalamic peduncle (ITP) immediately lateral to the mamillothalamic tract ipsilateral to the amygdaloid injection. As shown in inset 2, these axons follow a posterior intrathalamic course where they terminate in the dorsomedial thalamic nucleus. Note that a selective vascular lesion at the level of inset 1 would disrupt both the mamillothalamic tract and the inferior thalamic peduncle. Other abbreviations: ac = anterior commissure; as = arcuate sulcus; ca = caudate nucleus; cc = corpus callosum; cgs = cingulate sulcus; cp = cerebral peduncle; h = hypothalamus; hp = hippocampal formation; ic = internal capsule; ls = lateral sulcus; na = nucleus accumbens; oc = optic chiasm; ot = optic tract; ots = occipitotemporal sulcus; pu = putamen; rn = nucleus reuniens; rs = rhinal sulcus; sts = superior temporal sulcus.

TABLE 3. RESULTS OF NEUROPSYCHOLOGICAL TESTING

Case no.	Age (yrs)/sex/ handedness	Yrs of education	Occupation	Stroke onset	Stage of testing	Temporal orientation	WAIS-R		Language	Visuospatial abilities*	Executive control*	Personality changes
							VIQ	PIQ				
1	68/F/R	16	Retired educator	20.6.82	Acute	Defective	99	79	Nonphasic	2	2	Marked
					Chronic	Defective	117	93	Nonphasic	1	2	Marked
2	20/F/L	10	Homemaker	16.4.86	Acute	Defective	72	53	Nonphasic	3	2	Moderate
					Chronic	Intact	79	72	Nonphasic	1	2	Moderate
3	57/M/R	12	Farmer	31.1.86	Acute	Intact	96	117	Nonphasic	1	2	Moderate
					Chronic	Intact	93	119	Nonphasic	1	2	Moderate
4	58/M/R	12	Retired factory employee	5.2.86	No data available from acute stage							
					Chronic	Intact	88	88	Nonphasic	1	2	Moderate

* Interpretation scale: 1 = intact; 2 = mild to moderate impairment; 3 = severe impairment.

TABLE 4. VERBAL MEMORY

Case no.	Test stage	Rey Auditory Verbal Learning Test				Wechsler Memory Scale Logical Memory				Wechsler Memory Scale Paired Associates				Craik-Tulving Encoding			Release from proactive interference	Warrington Recognition Memory Test Words
				30 min delay														
		Trial 1	Trial 5	Recall	Recognition	Immediate		30 min delay		Immediate			30 min delay	Print	Rhyme	Semantic		
Maximum score		15	15	15	30	25	25	25	25	14	14	14	14	20	20	20		Scaled score
1	Acute	0	4		18	1	0			2	3	2	0					
	Chronic	3	5	0	15	9	6	0	0	5	6	6	4	0	0	0	Defective	5
2	Acute	1	3	0	5	1	0	1	0	2	2	2	2					
	Chronic	4	6	3	28	3	2	1	0	3	3	4	5	1	0	0	Defective	6
3	Acute	6	12	8	28	9	9	13	7	5	7	8	8	3	1	6	Defective	
	Chronic	7	14	8	29	14	11	9	11	8	10	12	14	5	12	14	Present	8
4	Acute	No data available from acute stage.								6	5	10	10	4	4	15	Present	10
	Chronic	6	12	8	30	11	10	11	8									

Abnormal scores are underlined.

TABLE 5. VISUAL MEMORY

Case no.	*Test stage*	*Benton Visual Retention Test*		*Rey Osterreith Complex Figure Test*		*Warrington Recognition Memory Test*
		No. correct	*No. of errors*	*Copy*	*30 min delay*	*Faces*
Maximum score		10	>9	36	36	Scaled score
1	Acute	1	20	21	1	
	Chronic	4	11	36	5	4
2	Acute	1	21	9	0	
	Chronic	4	12	29	8	7
3	Acute	5	4	36	13	9
	Chronic	7	5	35	20.5	5
4	Acute	No data available from the acute stage				
	Chronic	5	7	29	10	6

Abnormal scores are underlined.

1, despite having a college education and a high verbal IQ, scored worst on the Rey Auditory Verbal Learning Test and is the only patient to be defective in the recall *and* recognition components of this test. She is also defective on both the Warrington recognition tests. Case 2 scored normally on the recognition component of the Rey Auditory Verbal Learning Test. She also scored normally on the Warrington Recognition Memory Test for words and faces. In contrast, Cases 3 and 4 at the chronic stage scored in the normal range on all the verbal and visual memory tests except for those requiring delayed recall. The latter are the most difficult types of memory task, indicating that these 2 patients have a milder memory deficit than Cases 1 and 2. An exception to this general pattern is that Case 3 is defective on the Warrington Face Recognition Test.

All patients showed good motor learning (fig. 8).

Fig. 7 shows the scores on the remote memory test, 7A showing scores on the Boston Famous Faces test for spontaneous recall and 7B the scores using semantic and first name cues. Fig. 7C shows the results in recognition of recent events for Albert's test. Fig 7D and E show recall and recognition scores on Squire's test of famous events. All patients, but especially Case 1, benefited from cues on the Boston Famous Faces test and in the recognition format on the Squire's test. Only on this latter test on the recognition format does Case 1 show a temporal gradient scoring better in the 1950s compared with the 1980s.

These scores require qualification by the description of the performance of Case 1 on some of the tests as well as an analysis of 2 taped interviews, one in 1982 and another in 1988 and her answers in a written questionnaire about events in her personal biography.

First, on the recognition of famous faces it is noteworthy that the patient frequently was able to give the correct last name when given cues including the person's first name (fig. 7A, B). She also accurately identified by name all members of her family when shown pictures of them.

Secondly, in the interviews and biographical questionnaire the patient gave accurate information about her personal life, such as her date of birth, names of her schools

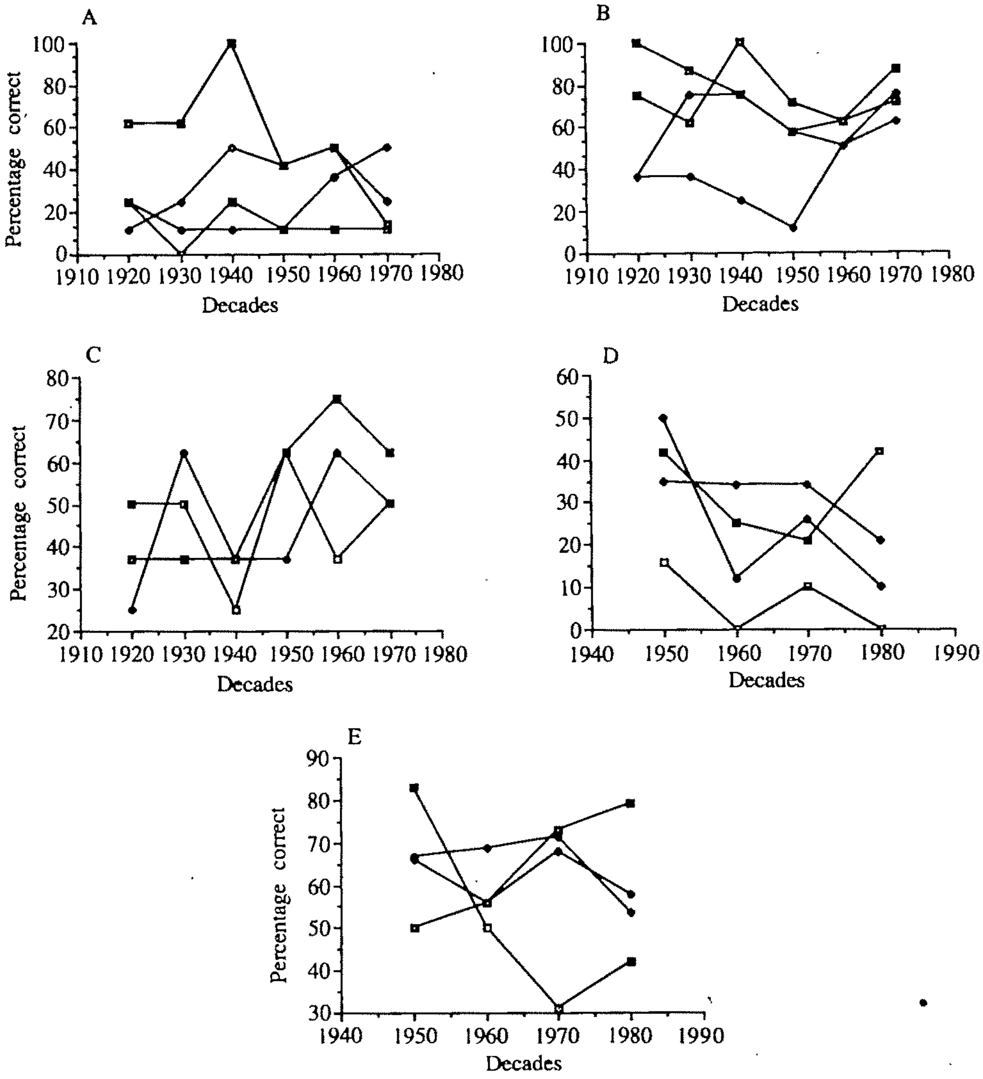

FIG. 7. A, scores by decade on recall of famous faces without cues (Boston Famous Faces Test, Albert *et al.*, 1979). B, scores by decade on recall of famous faces using both semantic and first name cues. C, scores on recognition of recent events by decade (Albert *et al.*, 1979). D, score on recall of recent events by decade (Squire *et al.*, 1989). This test was based on forms A and B and had 12 to 19 items per decade. The controls were 5 Iowans (3 females and 2 males) aged over 60 yrs. E, scores on recognition of recent events by decade (Squire, 1989). This test was based on a combination of forms A and B and had 12 to 19 items per decade. The controls were the same as for the recall component. In this test Case 1 shows a clear temporal gradient, scoring better in the 1950s than in the 1980s. Case 1 (⊡); Case 2 (◆); Case 3 (□); Case 4 (◇).

and colleges, names of people who influenced her, names of schools she taught at, age she started teaching, age and year she was married, date of death of her husband, names of her children and grandchildren, and acreage of her farm. An important characteristic of her performance was that she was greatly helped by the examiner orientating her,

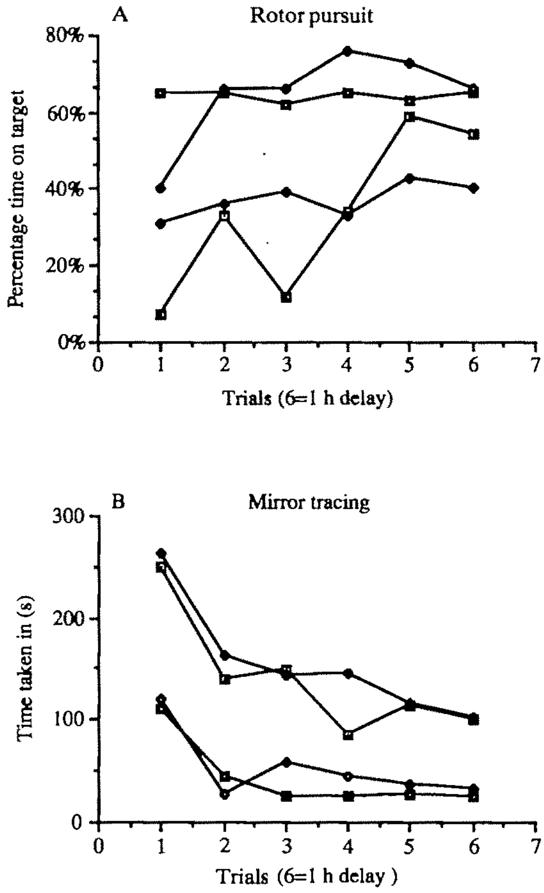

FIG. 8. A, motor learning in rotor pursuit. All patients except Case 3 showed improvement in the percentage of time on the target. Case 3 improved by having fewer episodes off target (not shown in graph). All patients maintained their improvement in the 1 h delay trial. B, motor learning on the mirror tracing test. All patients learned this task and maintained their learning at the 1 h delay trial. Case 1 (⊡); Case 2 (◆); Case 3 (□); Case 4 (◇).

for example, in 1982 she was asked who was President of the US and she said 'Lyndon B. Johnson'. When the interviewer said, 'No, it's later than that' she then replied 'Oh, Ronald Reagan'. When asked what her daughter did, she said that her daughter was the head nurse in Orthopaedics in a specific hospital (which she named) in Des Moines. The examiner pointed out that it was after that and the daughter had moved. The patient then gave the correct name of the current hospital in California to which her daughter had moved. When asked to name her grandchildren, she named the first 4 and when prompted that there may be another, she named the youngest. Another important point is that she gave no indication of learning about new events since her stroke. For example, she could not recall undergoing a colonoscopy even when the examiner tried to prompt her about this.

Case 2 was too young for the standardized remote memory tests to be of significance, but she performed well on a personal history questionnaire. Cases 3 and 4 performed normally on the remote memory tests and the personal history questionnaire.

In summary, Case 1 has a severe anterograde visual and verbal memory loss. Case 2 is also impaired but less so than Case 1. Cases 3 and 4 are only mildly impaired and not at all disabled by the deficits demonstrated in the laboratory. Motor learning was preserved in all patients. Remote memory loss was present in Case 1 as seen on spontaneous recall, probably normal in Case 2 (in view of her recall of biographical data), and normal in Cases 3 and 4. These findings on formal memory testing are in keeping with the observations of how the patients functioned in society after their stroke. Case 1 was completely disabled, Case 2 needed some supervision, and Cases 3 and 4 resumed their previous activities without any supervision.

DISCUSSION

Our findings support the notion that a significant anterograde amnesia resulted when there was damage to diencephalic neural systems related closely to both the hippocampus and amygdala, specifically the mamillothalamic tract and ventroamygdalofugal pathway to the dorsomedial nucleus (as in Case 1) and the mamillothalamic tract, anterior nuclei, anterior part of the dorsomedial nuclei, and superior part of the ventroamygdalofugal pathway (Case 2). (Note that the preservation of the ventral part of the ventroamygdalofugal pathway and most of the dorsomedial nuclei might account for this patient's better performance than that of Case 1.) When only one of these systems was damaged, a milder, clinically insignificant memory loss occurred (as in Cases 3 and 4). The role of damage to the midline nuclei or their medial temporal connections cannot be determined.

The second part of our study showed that the hippocampal and amygdala pathways are adjacent to each other anteriorly in the thalamus of the monkey (fig. 6c). Our plottings of the infarcts revealed that the lesions causing amnesia were also anteriorly located and involved the region where these pathways course adjacent to each other. In contrast, the lesions that did not cause a clinically significant amnesia were situated more posteriorly in the thalamus. It should be noted that the size of the infarct did not necessarily influence the occurrence of amnesia. Case 1 had the second smallest infarct and had the worst amnesia, whereas Case 3 had the second largest infarct and had a subclinical memory deficit. Furthermore, lesions involving dorsomedial nuclei alone did not cause a clinically significant amnesia.

CT findings in reported cases of infarction-related diencephalic amnesia

Von Cramon *et al.* (1985) summarized the CT findings of 11 diencephalon infarcts reported to cause amnesia; 6 were their own cases and 5 were from the literature. They noted that anteriorly located lesions cause amnesia, whereas posterior lesions do not, and concluded that the internal medullary lamina and the mamillothalamic tract were the critical sites of the lesions causing amnesia. Since then there have been several reports.

Gentilini *et al.* (1987) evaluated 8 cases with bilateral medial thalamic infarcts. All had acute CT scans between 4 days and 3 months, making it difficult to distinguish oedema from the chronic lesion. Case 5 could not be tested and Case 6 was an alcoholic. Case 2 had no acute verbal amnesia and the left-sided lesion was located posteriorly. Cases 4 and 8 recovered from their acute amnesia by 3 months; again the lesions were posterior. Case 1 had a documented amnesia at 3 months. The right lesion is clearly anterior but we are uncertain about the lesion on the left. Case 3 remained chronically amnestic according to the family and the lesions are probably anterior. Case 7 remained amnestic for several months in hospital; again the lesions are anterior. In essence it seems from the study that anteriorly located lesions are necessary for chronic amnesia. With posterior lesions, amnesia does not occur or the patients recover from it. This is in keeping with the authors' conclusion that the damage to the mamillothalamic tracts, anteriorly located structures, is related to the amnesia.

Mori *et al.* (1986) reported a case of left thalamic infarction and amnesia. Again the lesion was situated anteriorly and involved the mamillothalamic tract. Rousseaux *et al.* (1986) reported 5 cases of medial thalamic infarcts, 3 bilateral and 2 unilateral. They concluded that anterior medial thalamic lesions are more likely to cause amnesia than posterior lesions. Kritchevsky *et al.* (1987) reported 1 mainly left-sided and 1 right-sided thalamic infarct without chronic amnesia. The lesions were in the dorsomedial nucleus and did not involve the mamillothalamic tract, that is, they were posteriorly situated.

There are 2 relevant postmortem studies. Castaigne *et al.* (1981) reported the postmortem findings of 28 cases with paramedian thalamic infarction. Cases 2, 5, 7, and 13 had chronic amnesia and Cases 2, 5, and 7 had neuropsychological testing documenting this. Cases 5 and 7 had additional posterior cerebral territory infarctions which might have contributed to the memory deficit by involving the medial temporal area. The infarcts in Cases 2 and 13 involved the mamillothalamic tract (on the left in 2 and bilateral in 13). Again this suggested that anterior thalamic lesions are associated with amnesia. Bogousslavsky *et al.* (1986) reported a haemorrhagic thalamic infarct which did not involve the mamillothalamic tract and caused amnesia acutely. Because the amnesia was only noted acutely and the infarction was haemorrhagic, it is possible that there were pressure effects on anterior structures contributing to the deficits.

In summary, there are numerous reports of chronic amnesia from thalamic infarcts and the lesions are situated anteriorly. There are also several reports of thalamic infarcts without amnesia and the lesions are situated posteriorly. This is in keeping with the 4 patients we report here.

Primate studies

We will now review in the monkey the known afferent and efferent projections of the hippocampal formation and amygdala to selected diencephalic nuclei that have been thought to play a role in memory. Table 6 summarizes these projections as decribed in 6 studies. As can be seen, the anterior thalamic nuclei and mamillary bodies are strongly related to the hippocampal formation, whereas the dorsomedial nuclei are related to

TABLE 6. AFFERENT AND EFFERENT HIPPOCAMPAL AND AMYGDALA PATHWAYS TO AND FROM SELECTED DIENCEPHALIC NUCLEI IN THE NONHUMAN PRIMATE

	Anterior nuclei	*Mamillary bodies*	*Dorsomedial nuclei*	*Midline nuclei*
Hippocampal formation				
Afferent[1]*	+	0	0	+
Efferent[2]	++	++	0	+
Amygdala				
Afferent[3]	0	0***	0**	+
Efferent[4]	0	0	++	+

0 = no projections; + = mild to moderate projections; ++ = strong projections. [1]Amaral and Cowan (1980); [2]Rosene and Van Hoesen (1977); [3]Mehler (1980); [4]Nauta (1962); Aggleton and Mishkin (1984); Price (1986).

*Projections from the supramamillary nucleus to the hippocampus; **projections from dorsomedial nucleus to perirhinal cortex which then projects to amygdala; ***projections from supramamillary nucleus to amygdala.

the amygdala. The midline nuclei, including nucleus reuniens, are related to both hippocampal formation and the amygdala.

In summary, damage to the anterior thalamic nuclei, mamillary bodies and their connections is likely to impair a neural system related closely to the hippocampal formation, whereas damage to the dorsomedial nucleus or its connections is likely to impair neural systems related more intimately with the amygdala. At present, it is uncertain which system or systems that damage to the midline will affect.

Dense amnesia following lesions of the diencephalon and its connections

Lastly, we will summarize the occurrence of a dense amnesia in anatomically well documented lesions of the diencephalon and its connections, either in isolation or in combination. We will do this for man and monkey. Table 7 summarizes these findings. We should admit at the outset that whether there is a dense amnesia or not is a judgement we have made on the available data which is deficient in many instances; the patients with isolated fornix (Woolsey and Nelson, 1975), anterior thalamic (Mark *et al.*, 1970) and mamillary body lesions (Victor *et al.*, 1971), for example, had no formal neuropsychological testing but were all felt not to be amnestic. It would surprise us if on formal testing some deficit in memory functioning could not be documented in such cases. This is why we have used the term dense amnesia which we believe would be clinically obvious to the patients' families and their doctors. Furthermore, the monkeys with isolated lesions often showed mild impairment on memory tests compared with controls, but again these deficits were significantly less severe than monkeys with combined lesions.

Mair *et al.* (1979) and Mayes *et al.* (1988) carefully studied patients with Korsakoff's syndrome who came to postmortem and had only mamillary body and midline nuclei damage on gross inspection. As Table 5 shows, the midline nuclei have connections with both the hippocampus and the amygdala. Despite this, damage to this area alone, in the monkey, apparently does not cause severe amnesia (Aggleton and Mishkin, 1983*b*).

TABLE 7. AMNESIA IN ANATOMICALLY DOCUMENTED LESIONS INVOLVING THE DIENCEPHALON AND ITS MEDIAL TEMPORAL CONNECTIONS

	Presence or absence of dense amnesia	
Structures damaged	*Human*	*Monkey*
Isolated		
Fornix	No*[1]	No[2,3,4,5]/Yes[6]
Mamillary bodies	No*[7]	No[8]
Anterior thalamic nuclei	No*[9]	–
Ventroamygdalofugal pathway	–	No[5]
Dorsomedial nuclei	No[10]	–
Midline thalamic nuclei	–	No[11]
Combined		
Mamillary bodies, midline thalamic nuclei	Yes[12,13]	–
Dorsomedial nuclei, fornix	–	Yes[3]
Fornix, ventroamygdalofugal pathway	–	Yes[5]
Mamillothalamic tract, ventroamygdalofugal pathway	Yes[14,15]	Yes[17]
Anterior, dorsomedial, midline nuclei and fornix	–	Yes[16,17]

*No formal neuropsychological testing.

[1] Woolsey and Nelson (1975).
[2] Moss *et al.* (1981).
[3] Zola-Morgan and Squire (1985).
[4] Bachevalier *et al.* (1985*a*).
[5] Bachevalier *et al.* (1985*b*).
[6] Gaffan *et al.* (1984).
[7] Victor *et al.* (1971).
[8] Aggleton and Mishkin (1985).
[9] Mark *et al.* (1970).
[10] Kritchevsky *et al.* (1987).
[11] Aggleton and Mishkin (1983*b*).
[12] Mair *et al.* (1979).
[13] Mayes *et al.* (1988).
[14] Mori *et al.* (1986).
[15] von Cramon *et al.* (1985).
[16] Aggleton (1986).
[17] Aggleton and Mishkin (1983*a*).

However, in the postmortem studies of the two groups of Korsakoff's patients quoted above, damage to midline nuclei *and* mamillary bodies may be sufficient to cause amnesia. Again hippocampal and amygdala pathways could be involved.

In summary, patients and monkeys with isolated damage to one of the nuclei in the thalamus, or one of the medial temporal connections to these nuclei, are usually reported not to have a dense amnesia. In contrast, combined lesions invariably cause significant amnesia.

The diencephalon and memory

Thus from an anatomical point of view, we can conclude that (1) lesions located anteriorly in the thalamus are more likely to cause amnesia; (2) our tracing the ventroamygdalofugal pathway to the dorsomedial nucleus in the monkey showed that this pathway is lateral and adjacent to the mamillothalamic tract; (3) the lesions causing amnesia in our patients are likely to have interfered with pathways to the diencephalon both from the hippocampal formation (mamillothalamic tract) and amygdala (ventroamygdalofugal pathway). In contrast, in the 2 patients without significant amnesia the mamillothalamic tract was spared. All these observations support the idea that simultaneous damage to diencephalic nuclei and/or their connections related both to the hippocampal and amygdala is likely to result in a dense amnesia.

Other structures, however, such as hypothalamus, basal forebrain and medial frontal area have strong connections both to the medial temporal area and the thalamus and it is possible that pathways from these structures to the thalamus may also have been damaged by the infarctions and contributed to the amnestic state. In view of the experimental evidence in the monkey that damage to the ventroamygdalofugal pathway (at a site less likely to interfere with the above-mentioned pathways) and the fornix is sufficient to cause amnesia (Bachevalier *et al.*, 1985*b*), it is likely that interference in these two pathways by the lesions in our patients is also probably sufficient to cause amnesia without invoking damage to other pathways as mentioned above.

If it is true that damage both to amygdala and hippocampal systems in the diencephalon is necessary to cause a dense amnesia, it implies a certain parallel redundancy of the memory system which allows at least partial compensation when only one of the anatomical systems is damaged. This has been proposed by Mishkin (1982) and the findings in this paper are in keeping with this argument. There is, however, some contradictory evidence. Patient R.B. of Zola-Morgan *et al.* (1986) who had anoxic damage only in the hippocampal formation, had a clinically disabling amnesia. His memory did show mild improvement with time. In contrast, H.M., who probably has damage both to the hippocampus and amygdala bilaterally, had worse amnesia than R.B. (Zola-Morgan *et al.*, 1986) and has not improved with time. With regard to the diencephalon, the evidence to date is that damage to the diencephalic-related hippocampal structures alone (fornix: Woolsey and Nelson, 1975; Moss *et al.*, 1981; Zola-Morgan and Squire, 1985; Bachevalier *et al.*, 1985*a*; mamillary bodies: Victor *et al.*, 1971; and anterior nuclei: Mark *et al.*, 1970) does not necessarily cause a disabling amnesia. However, as pointed out earlier, the studies in man lack good neuropsychological measures of the amnesia and thus further studies in this area will be of great importance to clarify what at this time seem to be contradictory data.

The pattern of amnesia in our patients shows, as has that in others, that damage to the diencephalon may cause a marked anterograde verbal and visual amnesia. This is one of the first demonstrations of preserved motor learning in amnestic patients with thalamic infarctions (Nichelli *et al.*, 1988).

Case 1 had a temporal gradient (worse in the 1980s, better in the 1950s) on the Squire test of Recognition of Famous Events. This pattern differs from that described by Sanders and Warrington (1971) in a group of amnestics of mixed aetiology but is similar to several studies on patients with Korsakoff's syndrome (Squire *et al.*, 1975; Albert *et al.*, 1979). Winocur *et al.* (1984) studied retrograde memory in a patient with bilateral thalamic infarction and did not find the temporal gradient as seen in our Case 1. Thus because this pattern is seen in only 1 patient in our study and on only 1 test, and because of the contradictory available data, we do not believe any strong conclusion can yet be drawn from this finding.

There is some evidence from our observations in Case 1 and in the literature that the diencephalon may play a role in temporal orientation and the temporal sequencing of events. The first patient's memory was greatly improved when the examiner told her where in time she was; for example, as mentioned above, during an interview in 1982 she claimed Lyndon Johnson was President and when the examiner said it was later than that, she correctly named Ronald Reagan as President.

In 1956, Spiegel *et al.* reported that patients undergoing dorsomedial thalamotomy often suffered from 'chronotaraxis', i.e., disorientation for time. This occurred in 19 of 30 cases, 4 additional patients were disorientated for time and place, and 7 were not disorientated. In most instances the disorientation was short-lived. The transient nature of most of these cases makes it likely that other stuctures are also important in temporal orientation. In fact, we have observed that damage in the basal forebrain may result in disorientation-sensitive amnesia. For example, one of our patients (Damasio *et al.*, 1985), after sustaining damage in the basal forebrain from a ruptured anterior communicating aneurysm, during an interview several weeks after this haemorrhage denied being married. When orientated to this he correctly recalled a flood of information including his wife and children's names and their ages.

Experiments in Korsakoff's syndrome also support the notion that the diencephalon may be important in using time as a clue to remembering. Huppert and Piercy (1976) showed that patients with Korsakoff's syndrome are 'markedly impaired when required to make explicit judgements of temporal context'. These patients had greater difficulty identifying if they had seen pictures 10 min or 1 day before, than if they had seen the pictures at all. In another experiment, Squire (1982) came to a similar conclusion regarding Korsakoff's patients which he wrote 'were disproportionally impaired in the ability to make judgements about the temporal order of recent events'. He felt the deficit might be specific to the Korsakoff's patients because the same problem was not detected in a diencephalic amnestic (Case N.A.) and ECT patients who may have temporal lobe dysfunction after ECT. An alternative possibility is that Case N.A., who has an asymmetric diencephalic lesion may be better able to sequence events than Korsakoff's patients, who usually have bilateral lesions. Thus this finding of impaired judgement of temporal order may apply to diencephalic amnestics with bilateral lesions including Korsakoff's syndrome. This remains to be confirmed in future studies. Squire argued that this deficit was possibly related to frontal damage in Korsakoff's patients. All our patients had lesions which could compromise dorsomedial nucleus connections with the frontal lobe, which is in keeping with Squire's notion. Parkin and Leng (1988) also argued that Korsakoff's patients are particularly poor at making temporal discriminations. This was based on the performance of a group of Korsakoff's patients' performances on a learning task requiring recency judgements.

In conclusion, we have found that patients with bilateral medial thalamic infarcts in the interpeduncular profundus territory develop chronic amnesia when the lesions are anteriorly situated. This is in keeping with several other studies. These lesions can be small and strategically located to interfere both with the hippocampal-related neural systems such as the mamillothalamic tract and amygdala-related neural systems such as the ventroamygdalofugal pathway. A specific component of the latter that connects the amygdala to the dorsomedial thalamic nucleus is situated lateral but immediately adjacent to the mamillothalamic tract in the monkey. On review of the animal and human data of anatomically well described lesions affecting the diencephalon and its connections, together with the data from this study, we believe that, as in the temporal lobe, damage to diencephalic nuclei and/or their connections related both to the amygdala and hippocampus is more likely to cause a dense amnesia. We raise the possibility that the

P25699

diencephalon may be particularly important in temporal aspects of memory. Other characteristics of the amnesia are deficits in anterograde verbal and visual learning, retrograde amnesia, and preserved motor learning.

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CEREBRAL BLOOD FLOW, BLOOD VOLUME AND OXYGEN UTILIZATION

NORMAL VALUES AND EFFECT OF AGE

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SUMMARY

Regional cerebral blood flow (CBF), oxygen extraction ratio (OER), oxygen utilization ($CMRO_2$) and blood volume (CBV) were measured in a group of 34 healthy volunteers (age range 22–82 yrs) using the ^{15}O steady-state inhalation method and positron emission tomography. Between subjects CBF correlated positively with $CMRO_2$, although the interindividual variability of the measured values was large. OER was not dependent on $CMRO_2$, but highly negatively correlated with CBF. CBV correlated positively with CBF. When considering the values of all the regions of interest within a single subject, a strict coupling between $CMRO_2$ and CBF, and between CBF and CBV was found, while OER was constant and independent of CBF and $CMRO_2$. In 'pure' grey and white matter regions $CMRO_2$, CBF and CBV decreased with age approximately 0.50% per year. In other regions the decline was less evident, most likely due to partial volume effects. OER did not change or showed a slight increase with age (maximum in the grey matter region 0.35%/yr). The results suggest diminished neuronal firing or decreased dendritic synaptic density with age.

INTRODUCTION

Several studies concerning cerebral energy metabolism in vivo in healthy volunteers have been reported. Their aim was to determine the effects of age or to obtain normal values to compare with results in patients. The results have been partially conflicting and each new report seems to contribute to the confusion. Cerebral blood flow (CBF), cerebral metabolic rates of glucose (CMRglu) and oxygen ($CMRO_2$) are the functions which have been measured, either separately or in different combinations. Under physiological steady-state conditions CBF is coupled to the level of cerebral oxygen and glucose consumption (Sokoloff *et al.*, 1977). It is still unclear what mechanisms are responsible for the coupling between blood flow and energy requirements (Lou *et al.*, 1987).

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Both global and regional values have been determined using various techniques. Kety and Schmidt (1948) developed a technique using nitrous oxide to measure blood flow, oxygen and glucose utilization in brain globally. Kety (1956) reported a global decline of CBF, CMRglu and $CMRO_2$ with age. Most studies using in vivo techniques such as nitrous oxide, ^{133}Xe wash-out measurements or positron emission tomography (PET) show a decline of CBF with age. An exception is the study of Yamaguchi *et al.* (1986). With respect to oxygen or glucose utilization the situation is less clear: some studies have reported a decline with age (Kety, 1956; Kuhl *et al.*, 1982; Lebrun-Grandié *et al.*, 1983; Pantano *et al.*, 1984; Yamaguchi *et al.*, 1986), whereas others showed no such change (Duara *et al.*, 1983, 1984; De Leon *et al.*, 1983, 1984). Previous studies from our group (Frackowiak and Lenzi, 1982; Lenzi *et al.*, 1983) indicated a decline of $CMRO_2$ with age but with a more pronounced decrease of CBF.

Since these reports the ^{15}O steady-state technique has been refined through the introduction of a correction for intravascular signal in the $^{15}O_2$ scan (Lammertsma *et al.*, 1983*a*, *b*) and multiple arterial blood sampling during all scans (Lammertsma *et al.*, 1988). We now report new data using the improved oxygen-15 steady-state inhalation technique and PET in a group of 34 healthy subjects. We measured regional CBF, $CMRO_2$, OER (oxygen extraction fraction) and CBV (cerebral blood volume) to obtain normal values for comparison with our patient studies and to study the effect of age.

SUBJECTS

The group of healthy volunteers consisted of 16 female and 18 male subjects, who were equally represented across the age range (22–82 yrs; mean ± SD 45.1 ± 15.2; median 45). From the second to the sixth decades at least 5 subjects were included for each decade. In the seventh and eighth decades only 1 subject was available in each. The volunteers were recruited from hospital staff and relatives of patients studied in our clinical research protocols. The selection criteria were an unremarkable past medical and family history, no use of drugs, and a normal clinical examination with no signs of mental or physical abnormality. Only 1 examiner was involved in history taking and investigation. Neither CT nor MRI scans were performed. No standardized formal mental state questionnaire supplemented the clinical examination. The subjects were nonsmokers and had normal body weights.

Systolic and diastolic blood pressures were 121 ± 16 mmHg and 77 ± 10 mmHg, respectively. The pulse was 72 ± 11 per min. Blood samples were taken as part of the scanning procedure (*see* below) to measure haemoglobin, arterial oxygen content and pCO_2. The haemoglobin (Hb) concentration was 13.5 ± 1.1 g/dl, the arterial oxygen content 0.1835 ± 0.0140 ml/ml and the pCO_2 5.466 ± 0.324 kPa (41 ± 2.4 mmHg).

The project was approved by the Research Ethics Committee of the Hammersmith Hospital and permission for use of the appropriate radionuclides was obtained from the UK Administration of Radioactive Substances Advisory Committee. All volunteers gave their written informed consent.

METHODS

Radionuclides

The positron emitting radionuclides used in this study were oxygen-15 (2.1 min radioactive half-life) and carbon-11 (20.3 min radioactive half-life). The radionuclides were produced by a 16 Mev deuteron cyclotron, situated close to the scanning unit. The radiolabelled gaseous tracers ($C^{15}O_2$ and $^{15}O_2$) were produced 'on-line' (Clark and Buckingham, 1975) and continuously administered during the scanning procedure. The carbon-11 labelled tracer (^{11}CO) was produced in a batch before administration.

Scanning procedure

PET scans were performed using a whole body single slice positron emission tomograph (ECAT II, EG and G ORTEC) (Phelps *et al.*, 1978; Williams *et al.*, 1979). Data were collected in the medium resolution mode (FWHM = 16×16×16 mm). The ^{15}O steady-state inhalation technique was applied to measure regional CBF, CBV, OER, and $CMRO_2$. The advantages, limitations and improvements of the steady state inhalation technique have been described in detail elsewhere (Jones *et al.*, 1976; Frackowiak *et al.*, 1980; Lammertsma *et al.*, 1981, 1982, 1983*a*, *b*). In brief, the subjects sequentially inhaled trace doses of oxygen-15 labelled $C^{15}O_2$ and $^{15}O_2$ and carbon-11 labelled ^{11}CO through a small plastic face mask. The tracers were delivered continuously in a constant flow of air (0.5 l/min) and at a constant concentration for $C^{15}O_2$ and $^{15}O_2$; ^{11}CO was delivered as a bolus but in a constant flow of air. The radioactive doses of the delivered air were 20.8, 60.9 and 86 mCi/min for $C^{15}O_2$, $^{15}O_2$ and ^{11}CO, respectively. A plastic hood covering the face was connected to an air extraction device to remove to waste redundant and expired radioactivity.

The subjects were positioned on the scan couch without plugging the ears. They were instructed to close their eyes. Typically, 3 cross-sections (planes) through the brain were scanned. The 3 planes were chosen in relation to the orbitomeatal line (OM line) which was lined up with a laser beam after positioning the subject on the scanning couch. The lower plane (plane 1) was 2 cm above the OM line (OM+2) 'cutting through', the cerebellum. The middle plane (plane 2) was 4 cm (OM+4) and the higher plane (plane 3) 6 cm (OM+6) above the OM line, 'cutting through' insular grey matter and planum temporale, repectively. Adjustable cushions supporting both cheeks helped to keep the head immobile. The position of the head was checked throughout the scanning procedure with the help of a grid of light projected on the forehead of the scanned subject. With constant supervision, movement was immediately detectable. When deviations from the original position were noted, immediate correction was performed manually. Such corrections were rarely necessary.

When $C^{15}O_2$ is inhaled, rapid transfer of the oxygen-15 label to $H_2{}^{15}O$ takes place in the lung (West and Dollery, 1962). Continuous steady breathing of $C^{15}O_2$ results in a steady supply of radiolabelled $H_2{}^{15}O$ in the arterial blood, which distributes through the body. At steady-state, the level of $H_2{}^{15}O$ accumulated in a region of brain tissue in relation to that being delivered to the brain via the arterial blood is directly (although not linearly) proportional to the blood flow to that region (Jones *et al.*, 1976). When a steady-state was reached, usually between 8 and 10 min after the start of tracer inhalation, three 5 min emissions scans (each scanning the cross-sections (planes 1, 2 and 3) of the brain described above) were performed. Steady-state of brain radioactivity was checked using a continuous readout of the total count rate. Typically between 1 and 2 million counts were collected for each of the 3 planes. The total time that $C^{15}O_2$ was breathed amounted to 25 min. When data had been collected for plane 3, tracer administration was stopped. While the cerebral radioactivity decayed rapidly, the next tracer ($^{15}O_2$) was prepared and the procedure was repeated as for the $C^{15}O_2$ inhalation. At steady-state, the regional radioactivity in the brain during $^{15}O_2$ inhalation is determined by the oxygen extraction and its conversion into metabolic $H_2{}^{15}O$, recirculating $H_2{}^{15}O$ of metabolism, and intravascular $^{15}O_2$ (the fraction not extracted from haemoglobin) (Frackowiak *et al.*, 1980; Lammertsma *et al.*, 1981). Oxygen extraction can be calculated since it is possible to correct both for the recirculating water (using the $C^{15}O_2$ perfusion scan data), and for the intravascular component (an additional ^{11}CO scan; *see* below).

To correct the emission scans for tissue attenuation, transmission scans (330 s duration each) were performed using an external ring source of ^{68}Ge resulting in the collection of 5×10^6 counts per scan. The last part of the procedure consisted of breathing ^{11}CO tracer for 2–3 min. The tracer was then allowed to equilibrate (checked again using the chart recorder) in the blood compartment for about 4 min. This was followed by 5 min scans of each of the 3 planes. Typically, $200-300 \times 10^3$ counts per plane were obtained. Since ^{11}CO is bound to haemoglobin only, the measured regional brain radioactivity allows calculation of regional CBV by comparing tissue concentration of tracer to that in the arterial blood (Phelps *et al.*, 1979; Lammertsma *et al.*, 1983*a*, *b*; Pantano *et al.*, 1985) and subsequent correction of tissue OER for nonextracted intravascular activity.

The total duration of scanning, including transmission scan, was almost 2 h. The average effective dose equivalent for all subjects was 26.31 mSv (range 18.93– 38.53 mSv).

During both steady-state emission scans, 3 arterial blood samples were taken via a short radial artery catheter (Teflon-R gauge 21), which was inserted, using a long-acting local anaesthetic, before the scanning procedure. The taking of blood samples was painless and hardly noticed by the scanned subject. The samples (both whole blood and plasma) were measured in a well-counter that was cross-calibrated with the tomograph. An additional blood sample was taken during steady-state to determine blood gases (pCO_2, pO_2) pH and Hb content. The values obtained were used to calculate arterial oxygen concentration (ml/ml). During the ^{11}CO emission scans, 3 arterial blood samples in total were taken and whole bood radioactivity was measured in the well-counter.

DATA ANALYSIS

Reconstruction

After data collection, radioactivity distribution across the 3 planes was determined by a standard (filtered back projection) tomographic reconstruction technique resulting in quantitative images. All transmission and emission scans were reconstructed with the medium resolution reconstruction filter (16 mm FWHM) (Phelps *et al.*, 1978). Transmission scans were used to correct for tissue attenuation. After reconstruction of the radioactivity distribution, images were converted pixel by pixel into absolute units of blood flow, blood volume, oxygen extraction and oxygen utilization. This was achieved by solving the appropriate mathematical equations which relate cerebral tissue radioactivity to arterial blood radioactivity. CBF was expressed as ml blood/100 ml brain/min; CBV as ml blood/100 ml brain; OER as percentage, and $CMRO_2$ as ml oxygen/100 ml brain/min. For calculation of CBV a ratio of 0.85 (Grubb *et al.*, 1978) for small vessel versus large vessel hematocrit was used. $CMRO_2$ was calculated according to the formula: $CMRO_2 = CBF \times OER \times$ arterial oxygen content.

Regions of interest

After image reconstruction of the 3 planes and the calculation of functional distributions of CBF, OER, $CMRO_2$ and CBV, regions of interest (ROIs) were drawn in a standardized manner on a visual display unit. Fourteen ROIs, distributed over the 3 planes were determined (*see* footnote to Table 1) on the $CMRO_2$ image and subsequently transposed on the other functional images.

All ROIs (except the 'cortical ribbon' ROIs) were circular with a diameter of 8 pixels (= 20 mm). The left and right cerebellar, temporal pole, frontal cortex, occipital cortex and 'insular grey matter' ROIs were determined by placing the centre of the ROI over the maximum value for these territories on the right and left sides of the midline using a joystick. The 'insular grey matter' ROI (ING) is considered to be the purest sample of grey matter given the resolution characteristics of the tomograph. The position of the white matter ROIs was found by selecting the lowest value with lowest SD in anterior and posterior parts of the centrum semiovale between frontal and occipital lobe cortices in the highest plane (plane 3). The 2 ROI values were averaged to obtain right and left-sided white matter values.

Particularly for the occipital cortex and cerebellar ROIs care was taken to avoid proximity of venous sinuses. This was checked by inspection of the CBV scans.

The cortical ROIs were determined using a 'cortical ribbon' of small rectangular boxes (6×3 pixels each) placed by the computer on the images (*see* fig. 1). The rectangular boxes were plotted by the computer over the ribbon of peak values along the edge of the brain. Middle cerebral artery ROIs (MCA) were arbitrarily defined as the mean of 12 rectangular boxes located centrally in the 'cortical ribbon' on each

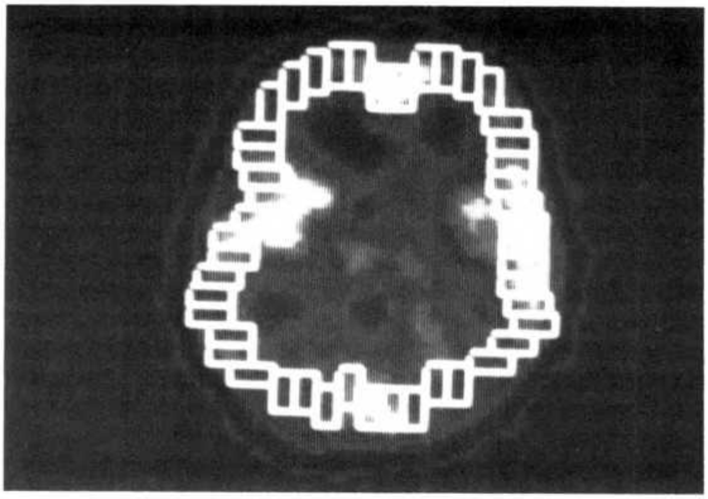

FIG. 1. Visualization of the 'cortical ribbon' as generated by the computer on the visual display unit. The several cortical ROIs are taken from this ribbon. *See* text for explanation.

side. The posterotemporal cortex ROI was defined as the 6 boxes on the middle plane (plane 2) 'cortical ribbon', starting posteriorly with the fourth box from the midline. The parietal cortex ROI was determined on the superior plane (plane 3) by taking 4 boxes, starting posteriorly with the fourth box from the midline. The parietal cortex ROI was determined on the superior plane (plane 3) by taking 4 boxes, starting posteriorly with the fourth box from the midline. No CT or MRI scans were available to compare the positions of the ROIs on the functional images. However, sufficient anatomical information is provided by the PET scan images to determine in a standardized manner the ROIs as described above (for discussion, *see* Duara, 1985).

Brain size

A brain size index was measured for each subject (Hatazawa *et al.*, 1987*a*, *b*) to be able to determine a possible influence of brain size on energy metabolism.

Statistics

The 4 functional values for each ROI were tabulated for the 34 subjects for right and left sides separately. Right and left hemisphere values were then averaged and regressions with age calculated. Regressions with age of the $\log_{10}$ values were also determined, yielding a percentage decrease per annum. In addition, for each ROI and each function, mean values and SDs were obtained across all subjects.

RESULTS

The mean values and SDs for each function calculated for all 14 ROIs (average of left and right sides) are given in Table 1. The values were not available for all 34 subjects in several categories. The actual number of measurements is also given in Table 1. The reasons for the missing values were twofold. On the one hand, it sometimes proved difficult or impossible to determine the localization of some of the ROIs, mainly in the white matter (Table 1). On the other hand, in some studies, because of technical difficulties, a steady-state could not be achieved or a CBV scan could not be obtained

TABLE 1. MEAN VALUES (±SD) FOR ALL SUBJECTS (LEFT AND RIGHT ROI VALUES AVERAGED)

	CBF	*$CMRO_2$*	*OER*	*CBV*
Plane 1				
CBL	49.4 ± 9.9 (n = 28)	3.37 ± 0.49 (n = 24)	39.9 ± 6.8 (n = 24)	4.7 ± 2.0 (n = 24)
TMP	35.7 ± 8.6 (n = 26)	2.26 ± 0.29 (n = 24)	38.7 ± 7.6 (n = 22)	6.6 ± 1.9 (n = 22)
Plane 2				
FRC	44.8 ± 10.4 (n = 33)	3.18 ± 0.46 (n = 32)	40.0 ± 5.9 (n = 32)	4.3 ± 0.8 (n = 32)
ING	54.5 ± 12.3 (n = 33)	3.69 ± 0.54 (n = 32)	38.5 ± 5.6 (n = 32)	5.2 ± 1.4 (n = 32)
OCC	46.8 ± 8.40 (n = 33)	3.59 ± 0.46 (n = 32)	43.2 ± 5.9 (n = 32)	8.6 ± 3.6 (n = 32)
BGN	42.4 ± 7.60 (n = 33)	3.07 ± 0.41 (n = 32)	40.4 ± 4.9 (n = 32)	3.5 ± 0.7 (n = 32)
MCA	44.3 ± 7.50 (n = 33)	3.11 ± 0.36 (n = 32)	39.8 ± 4.9 (n = 32)	4.7 ± 0.7 (n = 32)
HCX	42.8 ± 7.00 (n = 33)	3.11 ± 0.31 (n = 32)	40.9 ± 4.9 (n = 32)	5.0 ± 4.7 (n = 32)
PTC	38.0 ± 5.90 (n = 33)	2.96 ± 0.31 (n = 32)	43.4 ± 5.1 (n = 32)	4.7 ± 1.2 (n = 32)
Plane 3				
WMR	22.2 ± 4.90 (n = 29)	1.43 ± 0.24 (n = 28)	36.6 ± 5.3 (n = 28)	2.7 ± 0.6 (n = 28)
FRC	46.4 ± 10.7 (n = 29)	3.16 ± 0.44 (n = 28)	39.2 ± 6.9 (n = 28)	4.0 ± 0.6 (n = 28)
OCC	44.0 ± 7.60 (n = 29)	3.37 ± 0.42 (n = 28)	43.2 ± 7.4 (n = 28)	5.9 ± 1.7 (n = 28)
MCA	42.0 ± 8.00 (n = 29)	3.00 ± 0.41 (n = 28)	42.6 ± 6.4 (n = 28)	3.8 ± 0.5 (n = 28)
PAC	36.6 ± 6.60 (n = 29)	2.78 ± 0.32 (n = 28)	43.3 ± 6.7 (n = 28)	3.5 ± 0.4 (n = 28)

ROI descriptions: lower plane (plane 1: OM+2); CBL = cerebellum; TMP = temporal pole. Middle plane (plane 2: OM+4); FRC = frontal cortex; ING = insular grey matter; OCC = occipital cortex; BGN = basal ganglia; MCA = middle cerebral artery territory cortical ribbon; HCX = hemicortical ribbon; PTC = posterotemporal cortical ribbon. Higher plane (plane 3: OM+6); WMR = white matter; FRC = frontal cortex; OCC = occipital cortex; MCA = middle cerebral artery cortical ribbon; PAC = parietal cortical ribbon. n = number of available values for each ROI for the specified function.

during scanning of a particular plane, excluding the corresponding ROIs.

For the 'insular grey matter' ROI (ING of plane 2), 'white matter' ROI (WMR of plane 3) and 'cerebellar' ROI (CBL plane 1), the values are listed separately for all 34 subjects in Tables 2–4. The % SDs between the subjects for the grey matter ROI (ING) was 22.6 for CBF, 14.6 for $CMRO_2$, 14.6 for OER and 26.9 for CBV (Table 1). Fig. 2 shows, for one ROI, scatter diagrams correlating the four functions. $CMRO_2$ is positively correlated with CBF ($P < 0.001$) and CBF is negatively correlated wtih OER ($P < 0.001$). No correlation is apparent between $CMRO_2$ and OER ($P > 0.05$) and a weak positive correlation between CBF and CBV ($P < 0.01$). Fig. 3 illustrates the relationships between the four functions for all 14 ROIs in 1 individual (Subject 10) as an example.

Regression coefficients of the logarithmically-transformed values for the four functions in all 14 ROIs vs age are given in Table 5 yielding the percentage change per year. Scatter diagrams for the absolute 'insular grey matter' ROI are presented in fig. 4. For this ROI a significant decrease in $CMRO_2$ with age was found (0.0158 ml oxygen/100 ml brain/min/yr) paralleled by a significant decrease of CBF (0.257 ml/100 ml brain/min/yr) and CBV (0.046 ml/100 ml/yr). OER increased significantly with age (0.133/yr). The same changes with age were also found for the other ROIs, but statistical significance was reached only for some (Table 5).

Of note is that the cerebellar values did not show any change with age for any function.

TABLE 2. INSULAR GREY MATTER (ING-ROI) VALUES

Subjects	*Age (yrs)*	*CBF*	*CMRO₂*	*OER*	*CBV*
1	22	48.7	3.83	38.6	6.0
2	23	57.4	4.21	36.1	6.1
3	27	75.0	4.65	33.0	5.2
4	27	88.8	4.56	27.6	8.3
5	29	50.0	3.67	41.8	4.3
6	30	–	–	–	–
7	30	43.9	3.34	37.3	4.1
8	32	45.7	3.49	41.1	6.2
9	33	63.5	3.75	30.0	5.3
10	33	53.1	4.09	38.3	8.6
11	35	58.1	38.1	33.7	5.1
12	35	61.8	4.14	37.9	5.8
13	35	71.6	4.41	34.4	8.0
14	37	51.1	3.49	40.7	4.8
15	38	53.9	3.77	36.1	5.9
16	39	46.4	4.14	43.6	4.8
17	44	48.4	3.21	40.1	4.8
18	46	65.3	4.92	44.4	6.1
19	47	54.3	3.01	36.4	5.3
20	48	31.4	2.93	50.3	4.1
21	49	54.5	3.98	37.6	3.3
22	51	59.3	3.79	37.6	4.9
23	54	68.4	3.51	30.7	4.1
24	54	60.7	3.85	37.6	4.3
25	54	40.8	2.93	43.0	5.1
26	55	52.1	3.67	36.0	5.9
27	57	51.3	3.36	36.9	3.8
28	61	46.9	3.41	39.4	6.4
29	62	40.6	2.89	43.5	3.4
30	62	65.0	3.12	27.3	5.5
31	63	56.4	3.85	40.7	4.8
32	64	67.5	3.80	34.9	4.7
33	75	35.7	3.17	49.7	3.0
34	82	40.0	3.51	48.4	3.6

– = missing values.

The absolute values of the cerebellar ROI were the same on average as the 'insular grey matter' ROI (Tables 1, 2, 4).

Some 'cortical ribbon' ROIs (MCA, HCX and PTM) showed significantly higher values ($P < 0.01$) on the right side for CBF and $CMRO_2$, but no other consistent right-left differences were seen. No correlations were found between right-left differences and age. The average right-left ratio for OER was 0.999 ± 0.016 and for CBV 1.005 ± 0.03. For CBF and $CMRO_2$ these were 1.024 ± 0.034 and 1.021 ± 0.025, respectively.

The ratio of CBF/CBV (mean ± SD: 10.9 ± 2.6; Table 6), which is a measure of mean flow velocity (reciprocal of mean vascular transit time) and thought to be a useful index of perfusion reserve on the basis of studies in cerebrovascular disease (Gibbs *et al.*, 1984), did not change with age in any ROI (fig. 5B). Neither systolic nor diastolic blood pressure, nor pulse frequency, correlated with CBV or the CBF/CBV ratio in any of the ROIs. No clear correlations of Hb or arterial oxygen concentration values were

CALCUTTA CENTRAL

TABLE 3. WHITE MATTER (WM-ROI) VALUES OF ALL SUBJECTS

Subjects	*Age (yrs)*	*CBF*	*CMRO$_2$*	*OER*	*CBV*
1	22	26.1	1.69	33.4	3.37
2	23	–	–	–	–
3	27	24.4	1.53	35.6	3.42
4	27	20.8	1.59	37.1	2.94
5	29	–	–	–	–
6	30	27.7	1.95	36.2	3.59
7	30	18.7	1.33	42.4	1.87
8	32	21.6	1.44	39.8	3.22
9	33	33.1	1.64	27.7	3.66
10	33	18.1	1.54	40.9	1.71
11	35	24.8	1.55	41.3	2.22
12	35	21.0	1.33	35.4	2.47
13	35	17.2	1.26	36.1	2.19
14	37	31.4	1.73	29.3	2.86
15	38	32.9	1.56	28.3	2.16
16	39	24.6	1.29	32.7	2.4
17	44	22.7	1.49	38.9	2.18
18	46	20.1	1.45	40.7	2.78
19	47	27.0	1.54	34.9	3.09
20	48	22.5	1.7	39.0	2.6
21	49	–	–	–	–
22	51	–	–	–	–
23	54	–	–	–	–
24	54	21.5	1.27	31.8	2.89
25	54	23.2	1.14	27.9	2.43
26	55	17.5	1.27	36.9	3.01
27	57	23.3	1.74	38.6	1.73
28	61	18.1	1.05	34.4	2.59
29	62	22.8	1.32	32.3	2.68
30	62	23.9	1.38	34.9	2.22
31	63	14.2	1.33	50.4	2.92
32	64	16.1	1.09	37.4	2.7
33	75	16.2	1.34	44.3	2.74
34	82	16.1	1.11	39.6	2.22

– = missing values.

found with the four functions, although for CMRO$_2$ a significant positive correlation ($P < 0.01$) was found for ING and MCA ROIs. pCO$_2$ did not correlate with CBF across subjects. None of the physiological variables by themselves (pulse, blood pressure, Hb and pCO$_2$) showed dependence on age. Brain size did not correlate with the functional values of the ROIs except for global CBF ($P < 0.01$).

DISCUSSION

This study applies the steady-state oxygen inhalation technique, with multiple arterial sampling and correction of OER for nonextracted intravascular oxygen, to a new group of 34 healthy subjects. Normal values from the third to eighth decade for CBF CMRO$_2$, OER and CBV were established for 14 regions. Table 1 and fig. 2 show that the interindividual variability is wide, in the order of 15% for CMRO$_2$. This implies that

TABLE 4. CEREBELLAR TISSUE (CBL-ROI) VALUES OF ALL SUBJECTS

Subjects	*Age (yrs)*	*CBF*	*CMRO$_2$*	*OER*	*CBV*
1	22	–	–	–	–
2	23	–	–	–	–
3	27	50.4	–	–	–
4	27	52.8	–	–	–
5	29	–	–	–	–
6	30	43.9	–	–	–
7	30	72.9	–	–	–
8	32	56.0	3.95	42.0	3.61
9	33	52.9	3.13	32.9	4.16
10	33	45.9	3.86	40.9	4.61
11	35	59.2	3.25	36.0	3.58
12	35	50.2	3.17	35.1	6.00
13	35	42.0	2.98	34.9	6.15
14	37	49.1	3.35	36.1	2.98
15	38	56.7	3.72	39.1	6.01
16	39	52.6	3.19	37.5	7.11
17	44	76.7	4.81	37.2	10.25
18	46	41.2	3.36	46.2	3.56
19	47	38.9	3.36	52.2	6.21
20	48	47.9	3.19	34.4	4.33
21	49	–	–	–	–
22	51	–	–	–	–
23	54	–	–	–	–
24	54	38.7	2.79	43.9	3.75
25	54	52.9	2.96	31.8	4.26
26	55	38.7	3.14	40.9	4.11
27	57	44.0	3.13	36.7	4.31
28	61	50.1	3.00	35.1	3.47
29	62	45.7	2.85	35.0	3.83
30	62	57.0	3.73	39.4	3.60
31	63	36.3	3.95	58.3	4.88
32	64	43.9	3.86	47.7	4.85
33	75	47.9	3.51	39.4	7.33
34	82	37.5	3.00	44.7	6.20

– = missing values.

cohort comparisons with a patient group will only yield statistically significant differences when there are small but real changes caused by a disease if large groups are considered. At present this is not easily achieved in studies using PET.

It is obvious that the scanner available for this study did not allow a finer regional analysis such as is possible with the new high resolution multiple plane scanners now coming into use. Reasonable functional resolution between grey and white matter and major anatomically based regions was nevertheless readily achievable. The mean values found in our study correspond well with the literature values. For the 'grey matter' ROI (ING) the values were: CBF = 55 ml/100 ml/min; CMRO$_2$ = 3.70 ml/100 ml/min; OER = 38% and CBV = 5.2 ml/100 ml. The interrelationship between the four functions for the 'insular grey matter' ROI is shown in figs 2 and 3. CMRO$_2$ is not determined by CBF, but each value of CMRO$_2$ corresponds to a range of CBF values. Nevertheless a coupling between the two functions is observed across individuals.

TABLE 5. REGRESSION COEFFICIENTS OF LOGARITHMICALLY-TRANSFORMED VALUES VERSUS AGE

	CBF	*CMRO$_2$*	*OER*	*CBV*
CBL	−0.18	+0.05	+0.32	+0.53
TMP	−0.55	−0.22	+0.27	+0.34
FRC	−0.47*	−0.47**	+0.25	−0.53**
ING	−0.51*	−0.47**	+0.35*	−0.53**
OCC	−0.26	−0.21	+0.32*	−0.72
BGN	−0.10	−0.19	+0.19	−0.19
MCA	−0.29	−0.35**	+0.21	−0.46**
HCX	−0.26	−0.31**	+0.22	−0.43**
PTC	−0.06	−0.12	+0.21	−0.50*
WMR	−0.49	−0.64**	+0.07	−0.20
FRC	−0.56	−0.60**	+0.17	−0.33
OCC	−0.27	−0.18	+0.23	−0.06
MCA	−0.40	−0.50**	+0.12	−0.31*
PAC	−0.11	−0.22	+0.11	−0.26

* $P < 0.05$; ** $P < 0.01$. Units are in % change per year. *See* footnote to Table 1 for explanation of abbreviations.

A higher CMRO$_2$ is associated with a correspondingly higher rate of CBF values. CMRO$_2$ does not determine OER. The latter adjusts itself to the value of CBF, which may vary within a subject or differ between subjects due to alterations in breathing patterns or other physiological factors. The OER compensates reciprocally for different values of CBF. CBV was positively correlated with CBF within and between individuals. This indicates that the vascular space is larger where tissue perfusion is highest. Although care was taken to avoid placing ROIs close to venous sinuses, this was apparently less successfully done for the occipital ROI, resulting in an artefactually large value of occipital CBV (8.6±3.6%) (Table 1). The observed relations between CBF and CMRO$_2$, CBF and CBV, and between OER and CMRO$_2$ across individuals (fig. 2), become more evident when comparing the 14 ROI values in one subject (fig. 3). In addition, OER is then not dependent on CBF because of the close coupling of CBF to CMRO$_2$. It is remarkable how constant OER is across all regions in any one healthy subject's brain (fig. 5A and Table 6).

Global brain glucose utilization was reported to correlate with brain size (Hatazawa *et al.*, 1987*a*, *b*) but no such correlation was found in our data for CMRO$_2$, either for the specified ROIs or for total image values. For CBF, only global flow showed an inverse correlation with brain size ($P < 0.01$). We therefore did not adjust our values for a brain size effect.

In this study CBF, CBV and CMRO$_2$ decreased significantly with age in the frontal cortex and insular grey matter ROIs (Table 5). In other ROIs (white matter and cerebrocortical regions) CMRO$_2$ and CBV also decreased significantly. The decline in CBF in these regions did not reach significance, presumably owing to the larger variance of this variable. Nevertheless, a consistent negative trend of CBF decrease with age was observed for all other ROIs. OER showed a nonsignificant upward trend

TABLE 6. MEAN AND SD OF OER AND CBF/CBV FOR ALL ROIs IN EACH SUBJECT

		CBF/CBV		*OER*	
Subjects	*Age (yrs)*	*Mean*	*SD*	*Mean*	*SD*
1	22	10.5	2.8	41.1	3.48
2	23	9.0	3.3	44.3	1.80
3	27	9.6	2.4	39.9	1.81
4	27	8.5	1.9	40.9	2.66
5	29	7.1	3.2	43.7	1.82
6	30	9.2	2.1	45.5	5.38
7	30	9.9	1.2	43.6	2.95
8	32	9.1	2.8	43.4	4.48
9	33	11.2	3.0	28.2	3.21
10	33	9.4	2.4	44.9	1.77
11	35	10.0	3.5	41.4	5.13
12	35	9.6	2.0	38.8	3.94
13	35	8.3	2.5	38.9	3.74
14	37	12.3	3.5	34.2	1.99
15	38	12.9	2.6	35.6	3.18
16	39	11.3	2.8	36.0	4.12
17	44	11.3	2.7	39.9	2.60
18	46	9.4	2.9	46.8	2.37
19	47	8.9	2.9	44.8	4.08
20	48	9.0	2.5	37.7	2.55
21	49	8.3	2.9	43.2	4.81
22	51	7.3	1.7	40.7	3.89
23	54	9.2	2.1	31.0	2.72
24	54	9.4	2.4	43.9	5.15
25	54	10.8	1.7	31.2	1.20
26	55	8.6	1.7	40.1	2.56
27	57	6.7	2.1	37.2	–
28	61	9.9	2.9	39.7	3.10
29	62	9.5	3.1	37.5	4.10
30	62	10.4	2.2	40.2	1.78
31	63	6.3	1.6	56.1	5.61
32	64	9.4	2.9	49.2	4.47
33	75	7.2	1.9	46.3	3.53
34	82	9.1	1.9	46.1	2.05

– = missing value.

for all ROIs, except for 'pure' grey matter regions (ING and OCC), where the increase reached statistical significance ($P < 0.05$). Since OER essentially did not change in our study (fig. 5A), the decline of CBF and $CMRO_2$ with age (both approximately 0.5%/yr) must be coupled and does not appear to result from ischaemic factors. In addition, a parallel reduction of CBF and CBV was found. Thus the ratio CBF/CBV, which may be used to indicate perfusion reserve (Gibbs *et al.*, 1984) did not decrease with age (Table 6, fig. 5B). Since CBF determines the number of perfused capillaries (Diemer, 1968), our findings suggest that any loss of capillary density that might occur in the ageing brain is not in excess of decreased tissue energy demand. The increase with age of OER in the ING ROI would suggest that for that region additional vascular factors may play a role (for discussion, *see also* Frackowiak *et al.*, 1984). However, the OER increase was slight when compared with values seen in pathological ischaemic conditions (Wise *et al.*, 1983; Gibbs *et al.*, 1984).

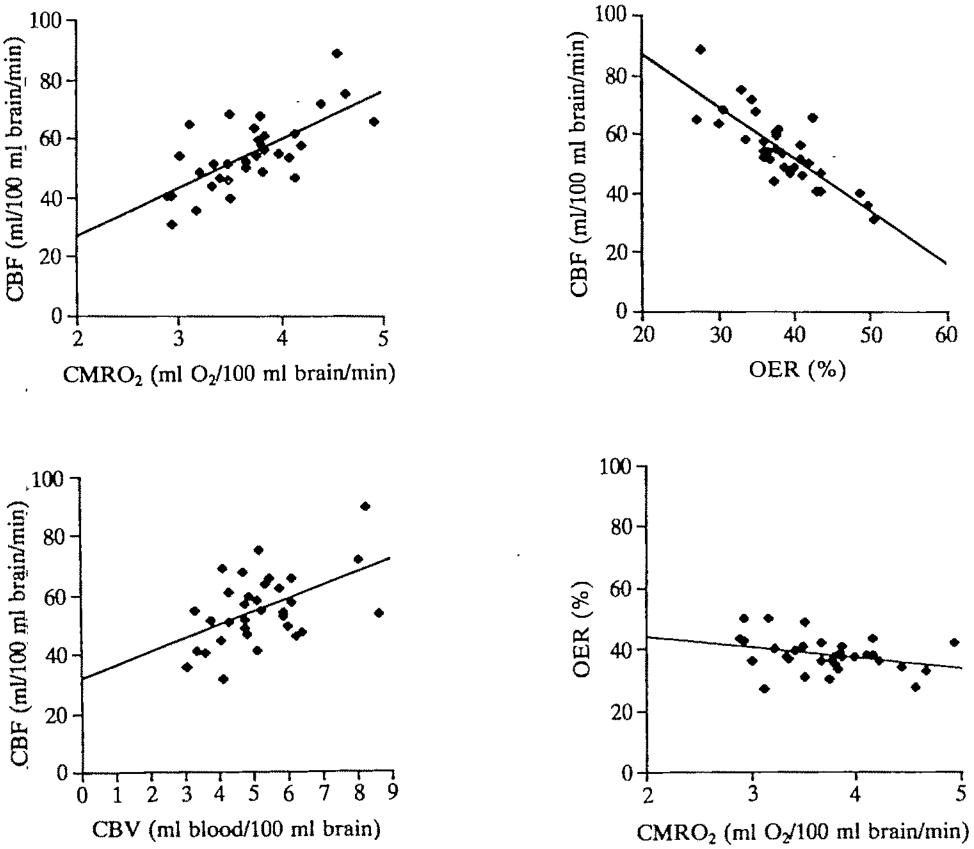

FIG. 2. Scatter-diagrams relating CBF to CMRO$_2$, CBF to OER, CBF to CBV and OER to CMRO$_2$. Each point is the value measured in a different healthy subject for the 'insular grey matter' ROI (ING). Linear regression lines were: CBF vs CMRO$_2$, $y = -5.4+16.2x$; $r = 0.69^{**}$; CBF vs OER, $y = 123-1.8x$; $r = 0.82^{**}$; CBF vs CBV, $y = 32+4.4x$, $r = 0.50^{*}$; OER vs CMRO$_2$, $y = 52-3.6x$, $r = 0.33$ (n.s.). ($* = P < 0.05$; $** = P < 0.01$; n.s. = not significant.)

We have compared our findings with results obtained using the steady-state technique without CBV correction for OER and with single arterial sampling (Frackowiak *et al.*, 1982; Lenzi *et al.*, 1983). CBF was reported to decline significantly with age but CMRO$_2$, although showing a downward trend, did not reach statistical significance. OER showed an upward trend. The absolute and relative decreases of CBF and CMRO$_2$ with age are similar in our previous and present reports. The findings are also of the same magnitude as the original hemisphere measurements revealed by Kety (1956), which also suggested a small increase of hemisphere arteriovenous (O$_2$) difference with age.

Equally, Pantano *et al.* (1984) showed that CBF and CMRO$_2$ declined with age. A significant linear correlation with age was only found for CBF. CMRO$_2$ showed a matched decrease, but significance was only reached when dividing the population into a 'young' and 'old' group. OER showed no statistically significant changes with age,

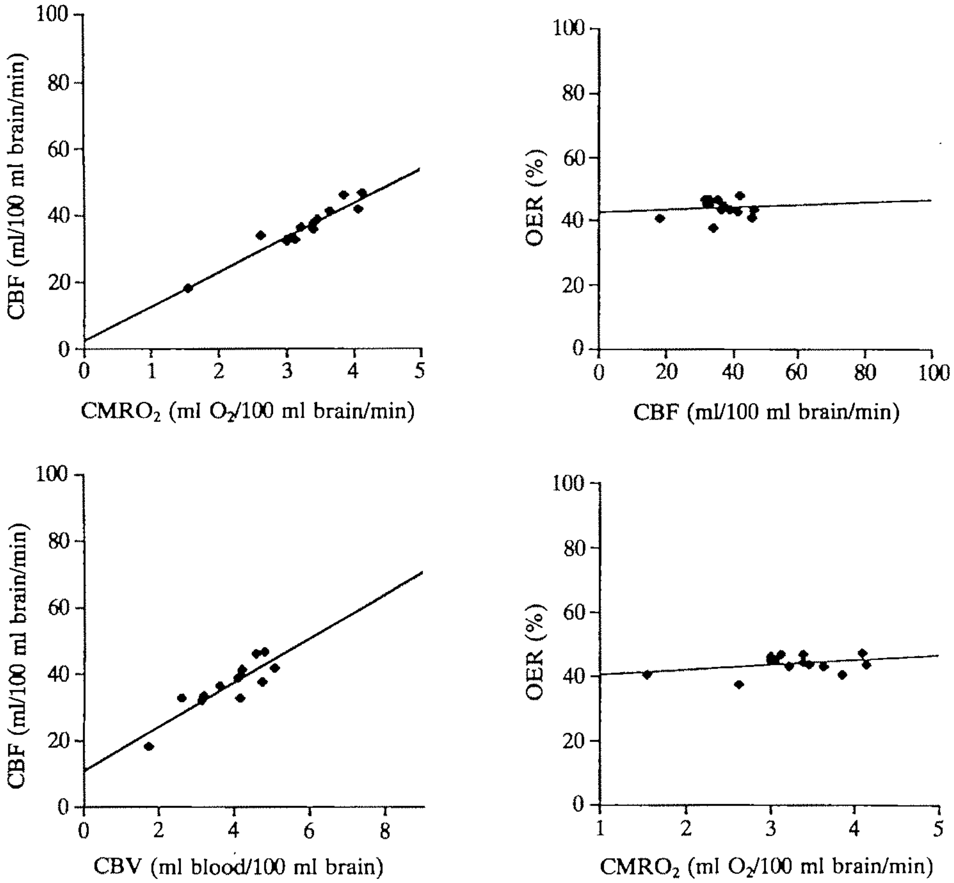

FIG. 3. Scatter-diagrams of relations between the 4 measured functions in all 14 ROIs in subject 10. Linear regression lines were: CBF vs $CMRO_2$, $y = 2.46+10.3x$, $r = 0.96^{**}$; OER vs CBF, $y = 42.6+0.037x$, $r = 0.09$ (n.s.); CBF vs CBV, $y = 11+6.6x$, $r = 0.88^{**}$; OER vs $CMRO_2$, $y = 39+1.6x$, $r = 0.38$ (n.s.). ($* = P < 0.05$; $** = P < 0.01$; n.s. = not significant.)

although a small upward trend was present. Because in that study the steady-state oxygen-15 inhalation technique was performed without CBV correction, OER, and thus $CMRO_2$, were slightly overestimated.

More recently, a study from Japan (Yamaguchi *et al.*, 1986), using the same technique as in the present investigation (including CBV scans), demonstrated a significant reduction with age for mean $CMRO_2$ in grey matter, but CBF and OER did not show any correlation with age. In several regions a significant decline of CBV with age was found. These results are difficult to interpret since it is unusual not to find a decrease of CBF with age, particularly in the light of a decline of $CMRO_2$. In such a situation a parallel decrease of OER would also be expected, but this was not found.

Measurements of cerebral glucose metabolism using FDG (^{18}F-fluorodeoxyglucose) PET scan techniques have yielded conflicting results in the literature. Kuhl *et al.* (1982)

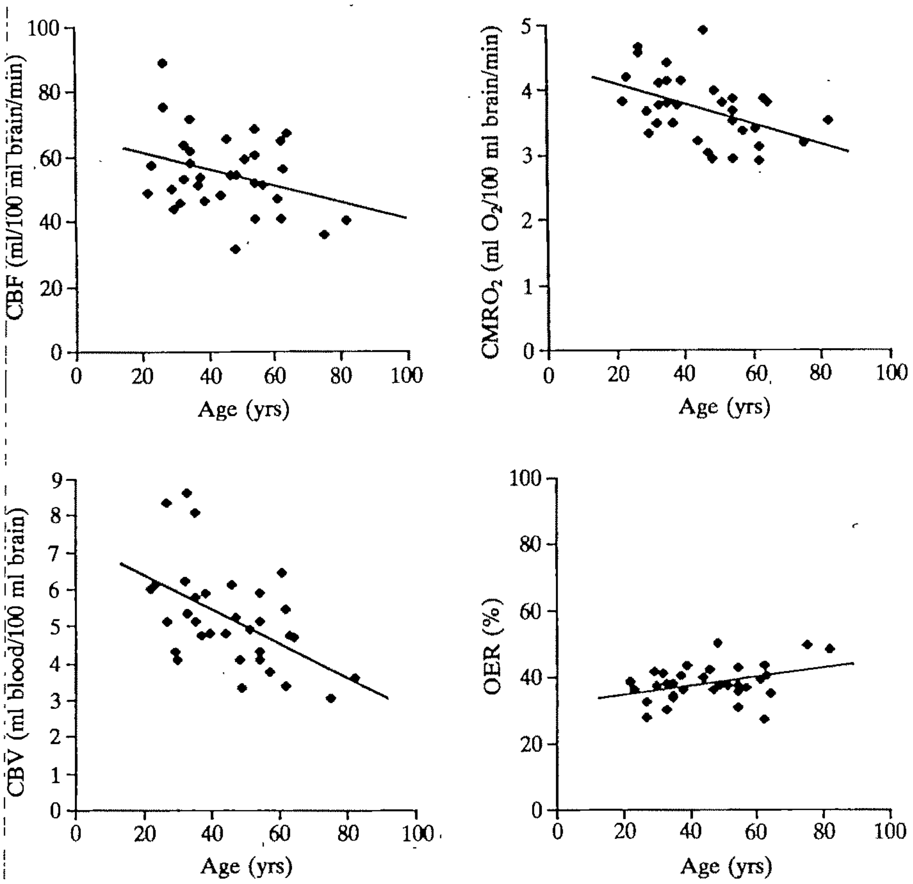

FIG. 4. Scatter-diagrams of absolute values for CBF, CMRO$_2$, CBV and OER against age for one ROI (ING) in 33 of the subjects. The regression equations are: $y = 66.5-0.26x$, $r = 0.35$* for CBF; $y = 4.42-0.0158x$, $r = 0.47$** for CMRO$_2$; $y = 32.2+0.13x$, $r = 0.37$ for OER*; $y = 7.3-0.046x$, $r = 0.52$** for CBV. (* = $P < 0.05$; ** = $P < 0.01$; n.s. = not significant). *See* Table 3 for significance of other regression coefficients.)

reported a decline of mean CMRglu with age. This decline was larger than for CMRO$_2$ previously reported (Lammertsma *et al.*, 1981). The authors suggested an altered utilization of substrates for energy metabolism in elderly subjects. This hypothesis had already been advanced by Sokoloff (1973) and Gottstein and Held (1979) using Kety-Schmidt techniques. The latter authors found a decrease of hemisphere CBF, oxygen and glucose consumption with age in 137 patients without neurological deficits. Glucose consumption decreased on average more than oxygen utilization, but the variance was large for both functions and the number of younger subjects was small. Dastur *et al.* (1963) also found that CBF, CMRO$_2$ and CMRglu are decreased in the healthy elderly and that A$-$V(O$_2$) tends to increase with age. However, the CBF and CMRO$_2$ changes were not statistically significant.

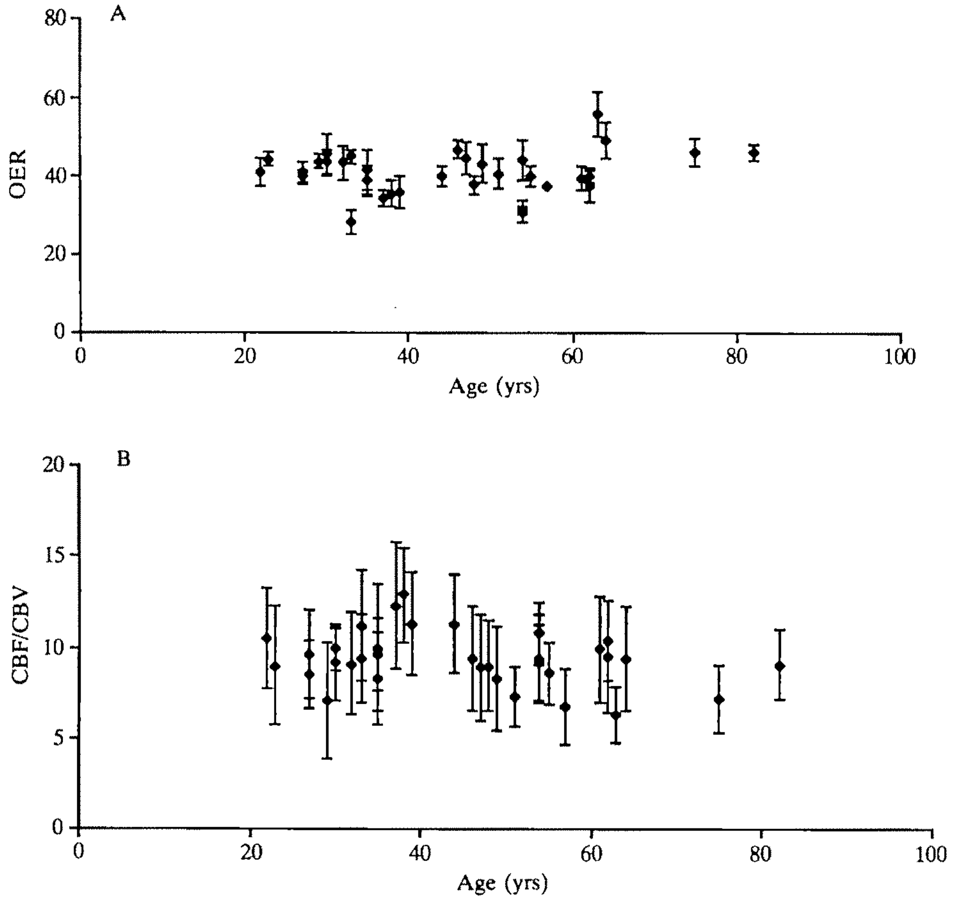

FIG. 5. A, mean and SD of all OER ROI values (minus white matter and cerebellar ROIs) for each subject plotted against age (linear regression: r = 0.27; n.s.). B, mean and SD of CBF/CBV for all ROIs in each subject plotted against age (linear regression: r = 0.19; n.s.).

Duara *et al.* (1984) and De Leon *et al.* (1983, 1984), using PET, showed no decline of CMRglu with age. These authors claim that careful screening of healthy volunteers had resulted in a particularly healthy group of elderly subjects. In our study, the subjects were evenly distributed according to age over several decades of life. On grounds of clinical and social history and clinical and neurological examination, the subjects in this study represent both completely healthy and asymptomatic elderly individuals. The blood pressure was not correlated with age, nor with the ratio CBF/CBV. This suggests that our subject population was not compromised by subclinical vascular disease. It is not clear who in the general healthy population should be considered to be 'really' healthy. The authors of the published reports to date differ in their opinion about this. It seems questionable whether more rigorous screening would yield a better or more representative sample of healthy people.

All our subjects were examined in the same resting condition, which is a more 'normal' state than the more artificial sensory deprivation used by other authors. Duara *et al.* (1983) suggested that sensory deprivation achieved in their studies by plugging ears and covering eyes did lower their measured values, particularly in the younger subjects. If this were true it would imply that energy metabolism in the brains of younger people is indeed different from that in elderly subjects. In a later study from the same group (Yoshii *et al.*, 1988) cerebral glucose utilization measured in a group of 76 subjects was reported. Mean cerebral glucose metabolism was significantly lower in the elderly group and appeared to be related to frontal, parietal and temporal reductions. Brain volume and atrophy was estimated using MRI in 58 subjects and accounted for 21% of the variance of the glucose utilization. When correcting the metabolic values for brain volume and atrophy, the effect of age or gender was no longer significant in their data. The authors suggested that the remainder of the measured metabolic values is probably due to differences in physiological arousal.

In contrast to the findings in the predominantly grey matter ROI (ING), we did not find an effect of age on cerebellar ROI values, although this region also contains predominantly grey matter, reflected in the high values for CBF $CMRO_2$ (Table 1). Hemisphere cerebellar atrophy in healthy elderly subjects has not been demonstrated on CT scans, although Koller *et al.* (1981) have reported selective atrophy of the cerebellar vermis with ageing. Counts of cerebellar Purkinje cells showed wide individual variations and a reduction of 2.5% per decade, after the sixth decade, has been reported (Hall *et al.*, 1975). Yamaguchi *et al.* (1986) found only a supratentorial decrease of $CMRO_2$. Kushner *et al.* (1985) reported in a short abstract no significant difference in cerebellar glucose metabolism between young and old healthy subjects. It is intriguing that the cerebellum apparently follows a different pattern of functional and anatomical change in life compared with the cerebral hemispheres.

In white matter, significant $CMRO_2$ decrease only was found, although CBF also decreased by 0.5% per year with age. No effect of age on white matter was found by Pantano *et al.* (1984) and Yamaguchi *et al.* (1986).

It is well recognized that partial volume effects play an important role, accounting for varying recovery of signal because of different shapes and sizes of brain structures in relation to the necessarily large ROIs (Mazziotta *et al.*, 1981). Basal ganglia ROI values are likely to have been influenced by the proximity of the lateral ventricles; the thinness of the parietal cortex inevitably results in a lowering of values in the corresponding ROI by white matter; and the temporal pole ROI may have been influenced by the surrounding skull. A related factor is the possible influence of brain atrophy on the values measured with PET. Moderate to gross ventricular enlargement can be detected on the functional PET images, but was not found in the scans presented here. Cerebral atrophy and ventricular dilatation have been reported by quantitative analyses of CT scans in healthy elderly subjects (Schwartz *et al.*, 1985). The degree and the age at onset of cerebral atrophy are variable. Correction for atrophy of the functional values obtained by PET scans has been suggested (Herscovitch *et al.*, 1986; Chawluk *et al.*, 1987). However, De Leon *et al.* (1984) found significant age-related atrophy on CT scans, particularly in the cerebral cortex, without changes in brain glucose metabolic rate measured with PET. This suggests that the normal ageing brain undergoes structural atrophic changes which are not necessarily reflected in regional functional activity. The same group (De Leon *et al.*, 1987) replicated these results using carbon-11 labelled glucose and a different tomograph. Although, after controlling for ventricular size, no age effect was found for the absolute values of glucose utilization, a relative hypofrontality was apparent in elderly subjects. Also, Yoshii *et al.* (1988) found that atrophy contributed only a small amount to the variance of cerebral glucose utilization in normal subjects. Equally, McGeer *et al.* (1986) did not find a correlation between brain atrophy and regional glucose metabolic rate in patients with Alzheimer's disease. However, CT measurements, particularly of cortical atrophy, may not be reliable enough to demonstrate a correlation with regional functional activity. The newer methods employing MRI scans promise to yield better comparisons. On the other hand, the noncorrespondence of CT-defined atrophy and PET measurements might be due to the fact that values in a ROI of a PET image are heavily influenced by tissue outside the delineated ROI. Only special regional corrections for atrophy of the PET values may provide valid comparisons. This issue was reviewed by Videen *et al.* (1988).

Energy requirements of the brain are determined in large part by processes such as membrane depolarization. These in turn are a function of cell membrane surface-to-volume ratio of the tissue (Mata *et al.*, 1980). Brain regions with high densities of nerve endings and dendrites will have high energy requirements and thus high $CMRO_2$ and CBF. Chugani *et al.* (1987) measured regional brain glucose utilization with PET in 19 children in several stages of development and found an anatomical and temporal pattern of glucose utilization paralleling neuronal and synaptic density. In human cortex neuronal cell losses and cell shrinkage with age have been reported by several authors (Henderson *et al.*, 1980; DeKosky and Bass, 1982; Anderson *et al.*, 1983). More recently, Terry *et al.* (1987) showed significant age-related decrements in large cortical neurons and a reduction of cortical thickness. However, the total number of neurons was unchanged because of an increase in the numbers of small neurons. Hence neuronal density remained constant. These authors suggested that shrinkage of neuronal cell bodies is a prominent finding in the ageing neocortex. A minor degree of neuronal loss was also detected when the cerebrum was considered as a whole. The changing nature of the neurons composing the cortex with age may be at the basis of the functional alterations assessed in vivo in this and other studies.

If for whatever reason loss of neurons within a sample volume (ROI) occurs, it will result in decreased energy metabolism within that ROI. If such a cell loss is accompanied by tissue shrinkage and the morphological phenomenon 'atrophy', then changes in $CMRO_2$ could parallel atrophy. We have shown a decline of $CMRO_2$ within an ROI with age and are not in a position to say whether the loss of 'functional activity' was accompanied by atrophy. If in atrophied brain tissue the remainder of the tissue has an unaltered neuronal density and composition, then $CMRO_2$ per gram tissue should be unchanged. If only selective cell loss or shrinkage occurs without atrophy, $CMRO_2$ will be decreased both in the ROI and per gram tissue. The newer dynamic PET tracer models for determination of rCBF are expected to provide in addition a measure of the regional volume of distribution of water. This should make it possible to approach the issue of atrophy and function direct.

There is clear evidence for age-related effects on brain neurochemistry, particularly in the dopaminergic and cholinergic neurotransmitter systems (McGeer and McGeer 1976; Allen *et al.*, 1983; DeKosky *et al.*, 1985). Effects of age on dopamine and serotonin receptors have been investigated by PET techniques in human living brain (Wong *et al.*, 1984). Receptor density in striatum and frontal cerebral cortex declined with age. These changes of neurotransmitter systems might equally be related to changes of the neuronal composition of cortex with age. Alternatively, these changes might be an expression of decreased activation by subcortical brain systems (DeKosky *et al.*, 1985). This may in turn result in decreased cortical energy requirement. Deactivation of the frontal cortex resulting in decreased energy metabolism demonstrated by PET has been suggested in the Steele-Richardson-Olszewski syndrome (D'Antona *et al.*, 1985; Leenders *et al.*, 1988). Our results as such cannot make a distinction between deafferentation or local cell loss as possible explanations for the decreased energy metabolism with age, but we favour the first mechanism.

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BRAINSTEM AUDITORY EVOKED POTENTIALS AND SOMATOSENSORY EVOKED POTENTIALS IN PONTINE HAEMORRHAGE

CORRELATIONS WITH CLINICAL AND CT FINDINGS

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SUMMARY

Electrophysiological studies were performed on 17 patients with pontine haemorrhage. Most had had massive hypertensive bleeding, leading to death in 12 of them within 3 months. Of the 5 surviving patients, 2 had a poor outcome and 3 a moderately good outcome. Brainstem auditory evoked potentials (BAEPs) and somatosensory evoked potentials (SEPs) were recorded in all patients, mostly with serial recordings. BAEPs were pathological in all patients. The most important finding was a reduction in amplitude or loss of waves. With a loss of waves after wave II bilaterally all patients died; the 2 patients with a normal amplitude of waves I–V at least on one side, survived in good condition. Further prognostic conclusions were not possible. The correlation with the clinical state was limited and was best for small unilateral tegmental haemorrhages. Eleven of the 17 patients suffered bilateral loss of the N20 component of the median nerve SEP. All these patients died. In patients with unilateral loss of the SEP the outcome could be favourable even if the bleeding extended across the midline. 'Subcortical' SEPs were not significantly altered. EEG findings in 15 and visual evoked potentials in 4 patients showed preserved forebrain electrical activity even in patients in poor condition.

INTRODUCTION

Pontine haemorrhage still has a poor prognosis (Goto *et al.*, 1980; Bewermeyer *et al.*, 1984) and therapeutic measures are limited. However, the wide use of CT has shown that in some patients with less severe brainstem syndromes a small pontine haemorrhage can be detected. Before the advent of CT these patients may have been suspected of suffering from ischaemic brainstem infarction. Thus a few patients may survive after a pontine haemorrhage (Kase *et al.*, 1980; Nakajima, 1983; Howard, 1986; Weisberg, 1986). Vascular malformations such as angiomas are more likely to produce smaller haemorrhages, whereas large haemorrhages are usually due to severe longstanding hypertension.

CT can easily detect a pontine haemorrhage. However, no precise prognostic factors are known to exist except for the fact that larger haemorrhages have a worse prognosis than smaller (Masiyama *et al.*, 1985). Evoked potentials have proved to be of

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prognostic value in other brainstem lesions. However, surprisingly few results of brainstem auditory evoked potentials (BAEPs) and somatosensory evoked potentials (SEPs) in patients with pontine haemorrhage are reported in the literature apart from single case studies (Stockard and Rossiter, 1977; Oh *et al.*, 1981; Chiappa, 1983; Hammond *et al.*, 1985; Portenoy *et al.*, 1985; Hashimoto, 1986). There has as yet been no study using SEP or BAEP or both in pontine haemorrhage with a larger number of patients. The purpose of this study was to investigate whether BAEP and SEP have prognostic value in pontine haemorrhage, and to correlate evoked potential findings with clinical signs and the localization of the haemorrhage by imaging techniques.

PATIENTS AND METHODS

We investigated 17 patients with pontine haemorrhage. All patients underwent CT and 4 also had MRI. Patients with cerebellopontine haemorrhages, and with purely midbrain or medullary bleeding, were excluded, but in some patients with large haemorrhages there was some extension from the pons into the midbrain. No considerable extension of a pontine haemorrhage into the medulla was observed. The average age of our patients was 51 yrs, with a range of 25–73 yrs. There were 12 males and 5 females. Twelve patients had suffered from severe hypertension for many years, but in 2 others hypertension was only discovered after the bleeding. Five had a previous history of alcohol abuse. One patient was being treated with warfarin and another had several metastases from a malignant melanoma. Twelve patients died within 3 months of the haemorrhage. One had a prolonged survival but had a tetraplegia and respiratory problems which required assisted ventilation. He died after 4 months. Another was at home but severely disabled, confined to a wheelchair, and spending most of his time in bed. He died 1 yr after his haemorrhage. In 3 patients there was only a slight to moderate neurological deficit with spasticity in all four limbs and ocular motor abnormality after 6 months.

All patients underwent BAEP and SEP investigations with serial recordings (an average of 3.5 per patient). In addition, the EEG was recorded in 15 patients and visual evoked potentials (VEPs) in 4 patients. Most of the patients were being treated in the intensive care unit. A neurological examination was performed before any electrophysiological studies. However, the neurological examination was sometimes limited by the fact that many patients were receiving sedative drugs because of assisted ventilation. When the signal/noise ratio was low, drugs blocking neuromuscular transmission were used in artificially ventilated and sedated patients. Thus nearly artefact-free records could be obtained for most patients.

BAEPs were elicited by monaural stimulation of an alternating polarity with 90–95 dB HL. This high click intensity was chosen as older patients often have badly defined waves I using lower click intensities because of high-frequency hearing loss. The effect of selective click stimulation with either rarefaction or condensation was only studied in certain cases. Stimulus duration was 0.1 ms and frequency 14.1 Hz. The contralateral ear was masked with white noise of 70–75 dB HL. Platinum needle electrodes were placed over the mastoids and the vertex. Ipsilateral and contralateral recordings were carried out simultaneously.

A total of 2000 sweeps was averaged with bandpass filters at 150 and 3000 Hz, 6 dB/octave. Latencies of waves I, III and V and the interpeak latencies I–V, I–III, III–V, III–V were measured and compared with normative data from our institute (±2.5 SD). The amplitude ratio V/I was calculated and considered to be pathological if the value was smaller than 1. Even if this ratio may occasionally be smaller than 1 in young healthy adults using high click intensities of 90–95 dB HL, it was always above 1 in our normal subjects older than 40 yrs; 16 of our 17 patients were in this age group. Amplitude of wave I is much more prone to age-dependent amplitude reduction than wave V. An amplitude ratio of less than 0.5 for waves III/I was defined as pathological.

SEPs after electrical stimulation of the median nerve at the wrist were derived simultaneously from the contralateral hand field (C3/P3 or C4/P4 according to the 10/20 system) and the lower spine (Cv7-Fz).

In some cases, further montages were studied (Erb's point; C2-Fz; Cz-contralateral shoulder; Cv7-'jugulum', i.e., anterior neck just above the sternum). The bandpass was 5 – 1500 Hz; 50 – 500 sweeps were averaged depending on the signal/noise ratio. Latencies of N13 of the 'spinal' potential and N20 were measured, as well as central conduction time between both peaks. An amplitude ratio N20/N13 of less than 1 and differences in amplitudes between the right and left cortical potentials of more than 50% were considered to be abnormal. The amplitude of the N20 potential was measured from the peak of N20 to the peak of P25. In those cases in which the N20 component was reflected in the Cv7-Fz derivation, the amplitude of N13 was measured from the peak to baseline.

The EEG was recorded according to the 10/20 system and VEPs from Oz to Fz using monocular or binocular flash stimulation with light-emitting diodes.

RESULTS

Brainstem auditory evoked potentials

BAEPs were pathological in all 17 patients with pontine haemorrhage (fig. 1). The predominant BAEP finding was a reduction in amplitude or loss of waves, whereas increased latencies with normal wave amplitude was less common. In initial recordings, normal waves I – III were found in 7 patients (8 ears). In most cases waves IV and V could not be distinguished from each other and were reduced in amplitude or occasionally delayed in latency. In some cases latencies of this wave complex were even shortened, so that the impression given was that of an isolated loss of wave V with preservation of wave IV (*see* fig. 4, right ear stimulation; an IPL III – V of 1.2 ms with a normal IPL I – III of 2.3 ms has never been observed in our control subjects). This interpretation was supported by the fact that both waves could not be seen separately on the contralateral recording. There was only one case with a very broad IV/V complex of high amplitude (fig. 1, Case 7) and another patient with delayed waves IV and V (fig. 1, Case 16). Normal waves I, and sometimes also waves II, with pathological waves III – V were found in 11 patients (17 ears). In most of these patients wave III was reduced in amplitude and waves IV and V were absent or could scarcely be seen.

In addition to the latter group there were 3 patients (5 ears) in whom only wave I was preserved, and no waves thereafter (fig. 1, Case 10). All 3 patients displayed spontaneous respiration and other preserved brainstem reflexes.

In Case 9 only some small waves were derived between 4 and 8 ms which could not be classified. In another patient, no BAEP could be obtained on either side, even at the initial recording. This patient was known to have had hearing loss before the haemorrhage, although he was not completely deaf.

In 8 patients the BAEPs were significantly different on the two sides whereas no differences or only minor changes were observed for the other 9. Differences in latency, amplitude or wave form could even be observed when comparing wave I on the two sides of 6 patients (fig. 1, Cases 1, 3, 5, 8, 11, 13).

Major differences of BAEP after different click polarities could be demonstrated in one patient (fig. 2). Rarefaction clicks evoked waves I – IV bilaterally. Although condensation clicks evoked 4 waves on the right and only 3 waves on the left, the result of alternating click stimuli showed only waves I and II on the left and waves I – IV

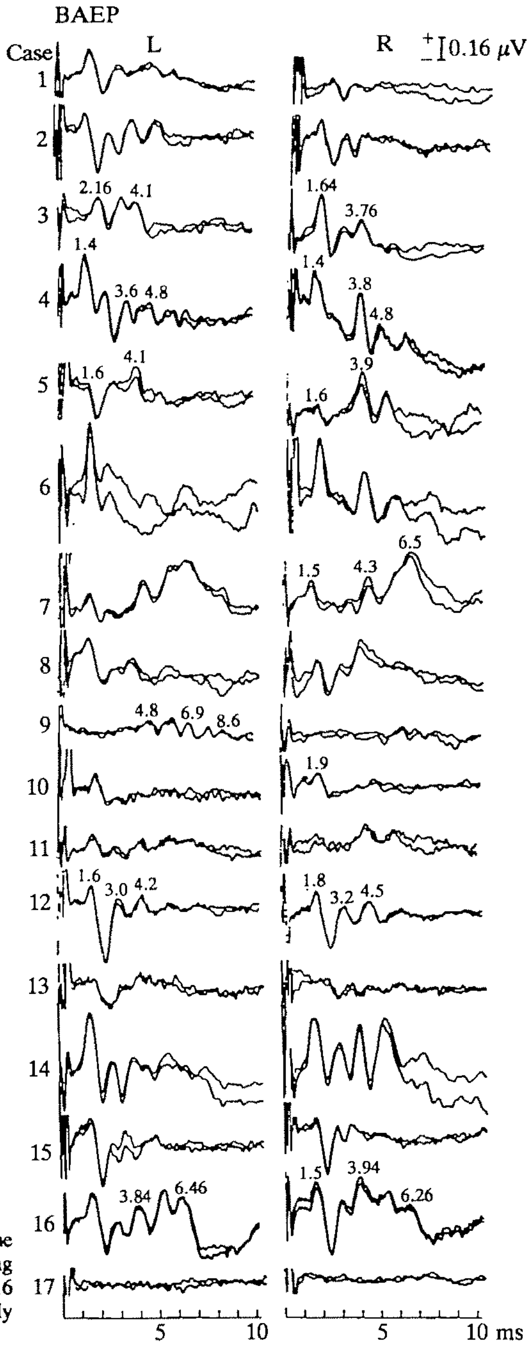

FIG. 1. BAEP findings for all 17 patients with pontine haemorrhage at the initial recording. There was preexisting hearing loss in *Case 17* (*lowest panel*). Cases 4, 14 and 16 made a good recovery and Cases 7 and 15 remained severely disabled. All other patients died within 3 months.

on the right. This effect was produced by considerable latency differences of waves II–IV to rarefaction-condensation stimulation on the right, whereas such latency differences were not present on the left. The CT scan in this case showed extensive

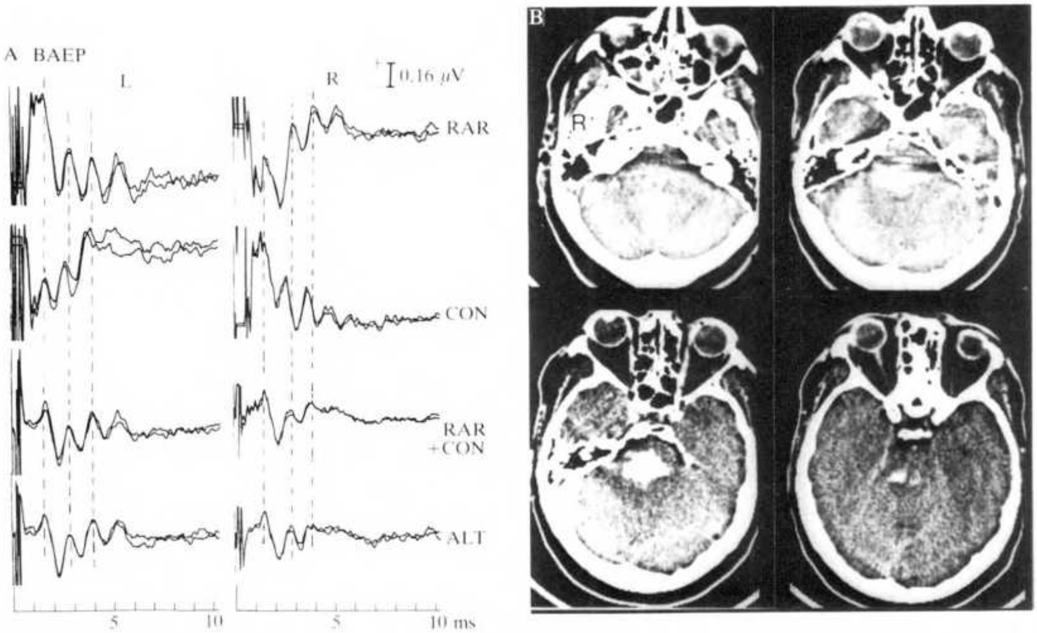

FIG. 2. *Case 2*, 45-yr-old hypertensive patient with tetraplegia, ocular bobbing and 'coma vigil'. A, BAEPs with alternating clicks in the lowest line show only waves I and II on the right. With rarefaction (RAR) and condensation (CON) clicks 4 waves can be seen. Different latencies of waves III and IV (V) after rarefaction and condensation lead to cancellation of these waves in the alternating mode. On the left the difference between rarefaction and condensation is even more pronounced. The third panel down shows the addition of panels 1 and 2 by computer; there is no difference from alternating stimulation. B, CT scans showing the pontine haemorrhage which spares the medulla oblongata and the midbrain.

bilateral bleeding with a slight preponderance to the right, sparing the most caudal part of the pons (fig. 2).

An exact correlation between BAEPs and neurological findings could not be detected. Severe BAEP abnormalities were found not only in tetraplegic patients but also in patients with only a moderate tetraparesis (fig. 3). They were found in patients who reacted to command (e.g., by ocular lid movements) and also in comatose patients. In the patient with the small haemorrhage in the left caudal pontine tegmentum, a left nuclear facial paresis, a one and a half syndrome and right hemihypaesthesia and hemiataxia correlated well with normal waves I and II and severely altered waves III–V to the left ear stimulation (fig. 4). The significance of the additional loss of wave V on the right will be discussed later.

All patients who displayed loss of potentials after wave II bilaterally died. Both patients with normal amplitudes of waves I–V at least on one side survived. However, in the other BAEP pattern the prognostic value was somewhat vague: some patients died and others survived.

Two different types of change could be observed in BAEP serial recordings. In some patients the BAEP indicated a change in brainstem function, leaving wave I unchanged

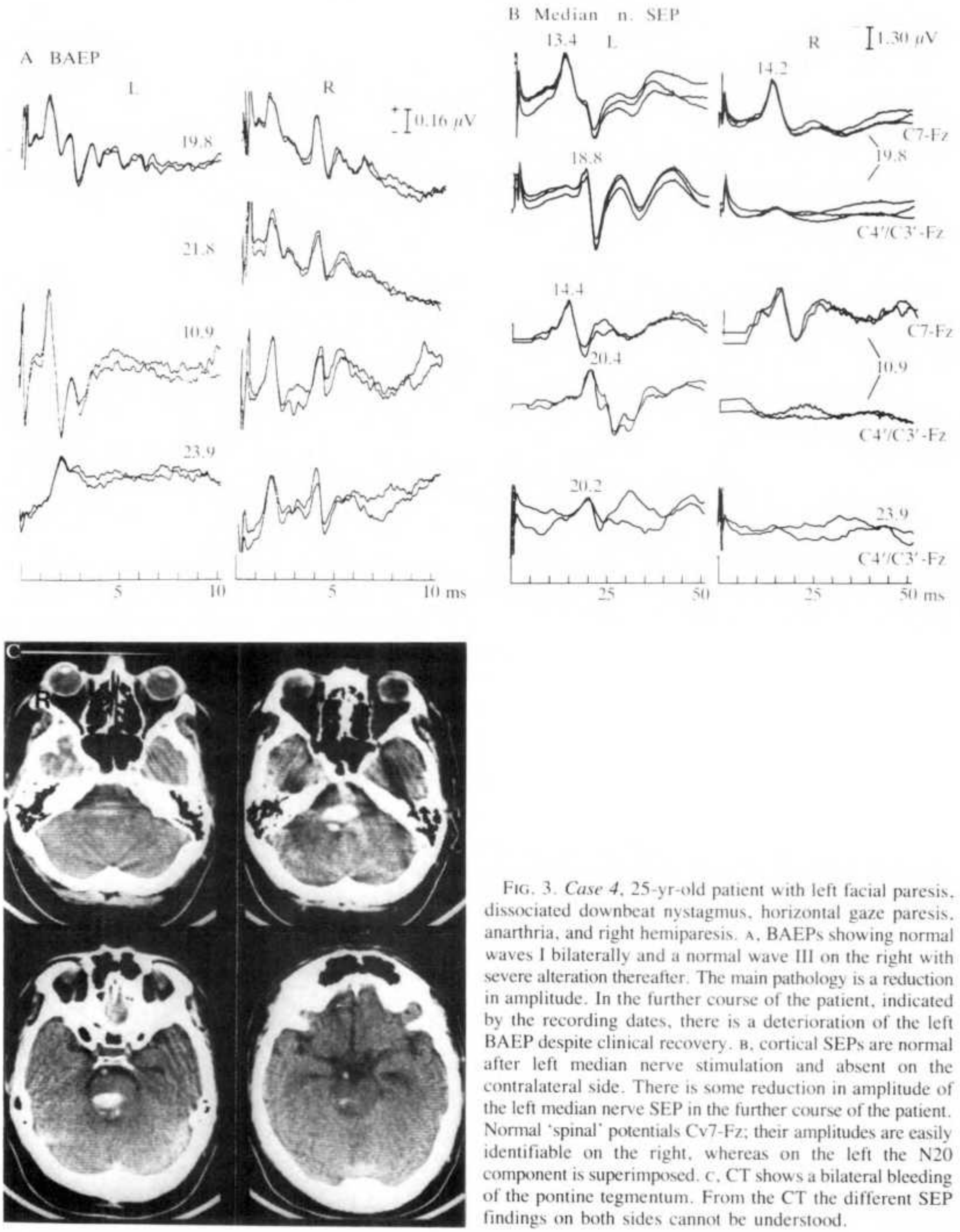

FIG. 3. *Case 4*, 25-yr-old patient with left facial paresis, dissociated downbeat nystagmus, horizontal gaze paresis, anarthria, and right hemiparesis. A, BAEPs showing normal waves I bilaterally and a normal wave III on the right with severe alteration thereafter. The main pathology is a reduction in amplitude. In the further course of the patient, indicated by the recording dates, there is a deterioration of the left BAEP despite clinical recovery. B, cortical SEPs are normal after left median nerve stimulation and absent on the contralateral side. There is some reduction in amplitude of the left median nerve SEP in the further course of the patient. Normal 'spinal' potentials Cv7-Fz; their amplitudes are easily identifiable on the right, whereas on the left the N20 component is superimposed. C, CT shows a bilateral bleeding of the pontine tegmentum. From the CT the different SEP findings on both sides cannot be understood.

(figs 3, 4). Again, BAEP changes corresponded mostly to clinical changes, but there were exceptions, where the BAEP showed deterioration despite the clinical improvement of the patient (fig. 3). In other patients there was a gradual deterioration of the potentials

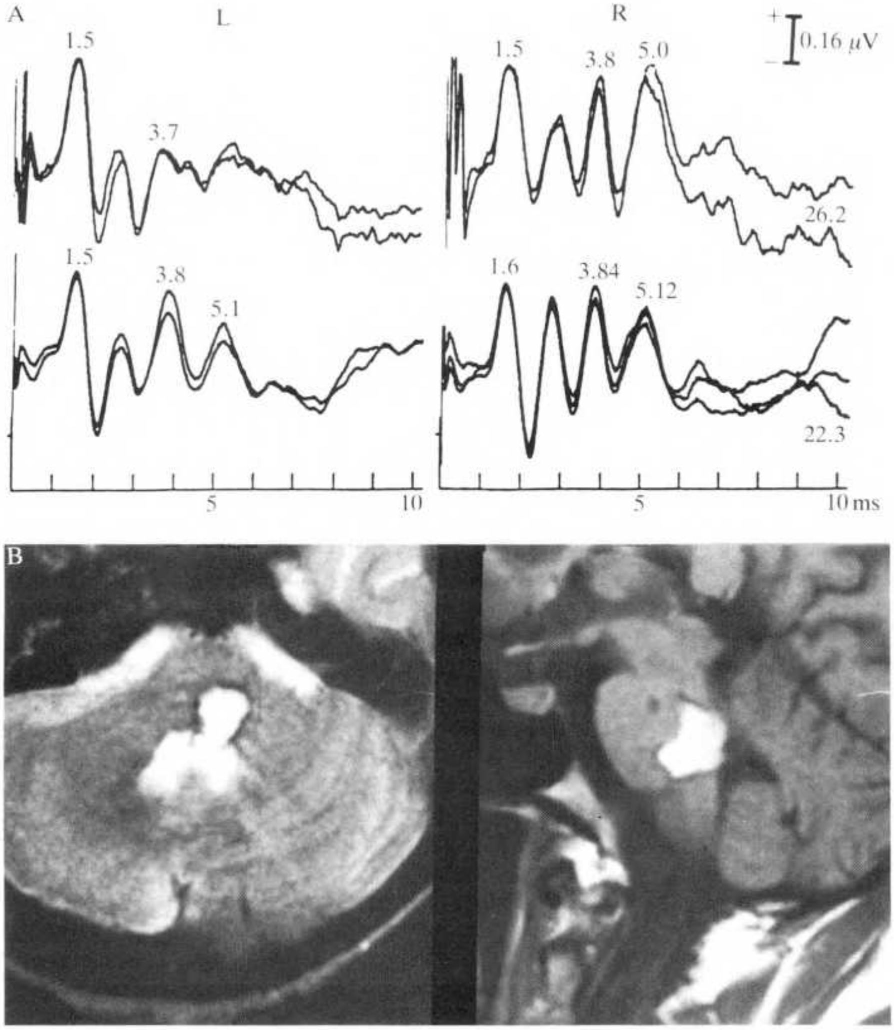

FIG. 4. *Case 14*, 41-yr-old female with left nuclear facial paresis, a 1½ syndrome, right hemihypaesthesia and hemiataxia on admission. A, BAEP 10 days after the haemorrhage (*upper traces*) show an alteration after wave II on the left. On the right the short IPL III−V of 1.2 ms suggests an isolated loss of wave V. There is considerable improvement of the left BAEP about 1 month later (*lower traces*). SEPs (not shown here) were preserved after left median nerve stimulation and absent on the contralateral side. This patient made a good recovery. B, MRI showing haemorrhage into the left pontine tegmentum (*left*: lower pontine level; *right*: left parasagittal plane).

including wave I (fig. 5), thus preventing an assessment of brainstem functions.

Two patients whose CT showed strong lateralization of the haemorrhage also had clearly different BAEP findings between sides. But there were also right-left differences of the BAEP in patients whose haemorrhage showed only slight or no lateralization on the CT. With regard to localization in the craniocaudal direction, it could not be predicted with any certainty whether the pathology of the potential would begin after

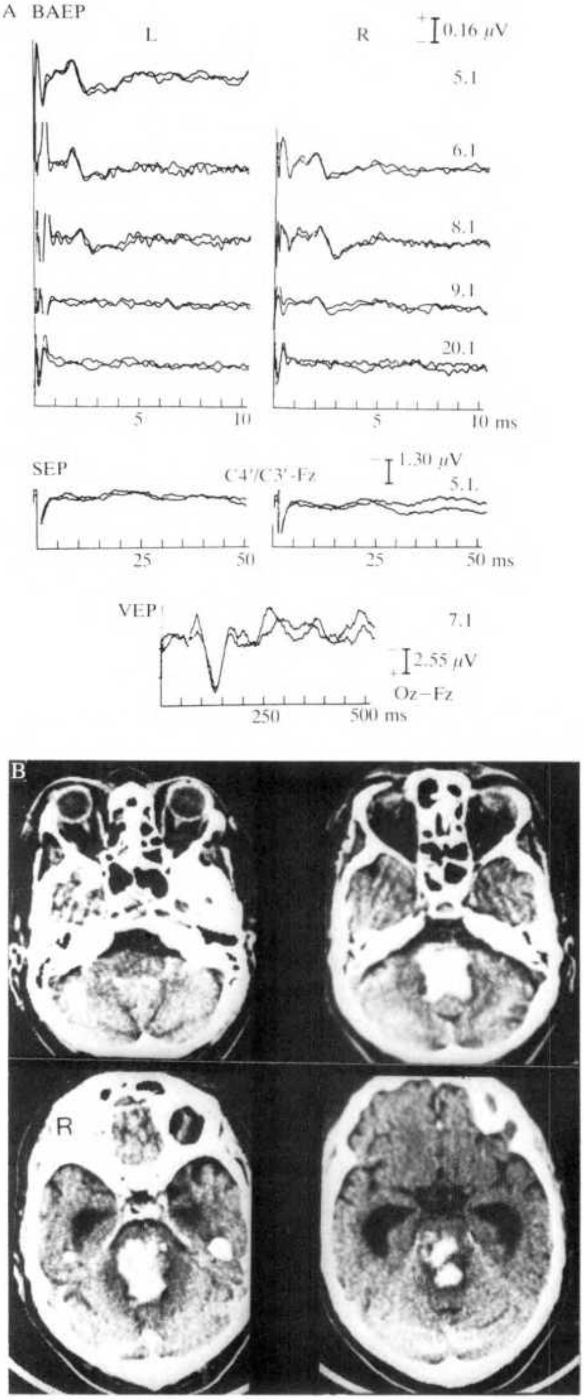

FIG. 5. *Case 10*, a 30-yr-old man in coma and tetraplegia on admission with slight improvement to coma vigil over the following days. A, BAEP showing only wave I bilaterally. Despite slight clinical improvement, wave I disappears in later recordings which may also be due to audiological factors. The patient died from cardiac arrest and was never 'brain dead' during the preceding course of his illness. Cortical SEPs (*lowest pair* of traces) were absent and VEPs (*lowest panel*) well preserved. B, CT showing massive pontine haemorrhage with extension to the midbrain and dilatation of the temporal horns of the lateral ventricles.

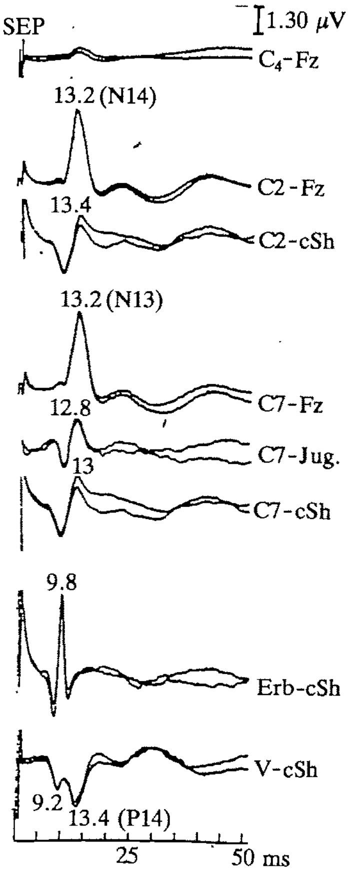

FIG. 6. *Case 3*, left median nerve SEP in a patient with a large bilateral pontine haemorrhage. The N20 component of the SEP is absent bilaterally. The additional recordings of subcortical SEPs show preserved N13, N14 and P14 peaking at 13.2 – 13.4 ms. There are no major alterations of these subcortical SEP components which are consistent with their being generated below the pons. cSh = contralateral shoulder.

wave II or wave III from the CT. However, sagittal CT reconstruction or MRI were only available for a few patients.

Somatosensory evoked potentials

In 11 of the 17 patients cortical SEPs were absent bilaterally in the initial recording (fig. 5). In 8 of these patients the potential from the lower cervical spine (Cv7-Fz) was normal, in 2 patients it was moderately delayed due to a preexisting peripheral neuropathy, and in 1 patient it could not be assessed due to artefacts. Further montages to derive subcortical SEPs in some patients did not show a clear abnormality. In fig. 6 (lowest line) the P14 is not separate from P13. However, this pattern may also be observed in controls, and the finding can only be considered abnormal if earlier recordings show separation of these two waves.

Unilateral preservation of the cortical SEPs was found in 3 patients and bilateral preservation in 3 patients. One of the latter patients re-bled, leading to bilateral loss of the SEP. In all except 2 patients, the amplitudes of cortical SEPs were reduced with regard to the amplitude ratio N13/N20. Central conduction time (CCT) was normal (fig. 3) in all cases in which it could be determined.

All 11 patients with bilateral loss of cortical SEPs died after a period of between a few days and 3.5 months. Some of them regained some consciousness after the initial coma. They were tetraplegic with horizontal or total gaze paresis and had their eyes open, but with a delayed reaction to command, despite absent cortical SEPs. Such a finding with bilateral loss of cortical SEPs was never reversible, and not even transient. This was also true when the bleeding had resolved and only a small defect remained visible on the CT scan. On the other hand, of the 6 patients with unilateral or bilateral preserved SEPs, 3 made a fairly good recovery; 1 remained severely disabled at home; 2 patients died; 1 of them had bilaterally preserved SEPs prior to rebleeding which finally led to loss of SEPs. Unilateral preservation of the SEP could be found not only with unilateral haemorrhages (fig. 4) but also when the haemorrhage transgressed the midline of the pons (fig. 3).

Electroencephalography

EEG findings were available for 15 patients. There was no correlation either with the prognosis or with the clinical state. The findings displayed a (mostly slow) alpha rhythm in 10 patients, mixed alpha-theta activity in 3 and theta activity in 2, in most cases without desynchronization to visual stimuli. In some cases, serial recordings showed a progressive slowing of the activity.

Visual evoked potentials

In those 4 cases with VEP recordings, these were normal to flash stimulation. All patients had severe neurological deficits. This was also observed when the patients were tetraplegic and had only wave I preserved bilaterally in the BAEP (fig. 5).

DISCUSSION

All our patients showed gross abnormalities in their BAEPs. This can well be explained by the location of the BAEP generators in the tegmentum of the upper medulla and the pons (Scherg and von Cramon, 1985). BAEPs are thus very sensitive for the detection of pontine bleeding. This sensitivity is even higher when compared with basilar artery thrombosis, where 18% of 56 investigated ears in 28 patients showed normal BAEPs (Ferbert *et al.*, 1988). Basilar artery thrombosis may lead to infarction limited to the pontine base leaving the auditory pathways intact, whereas sparing of the tegmentum is very unusual in pontine haemorrhage and was not observed in our patients, nor in the 10 patients of Kushner and Bressman (1985) or the 24 cases with autopsy reported by Nakajima (1983).

The specificity of the BAEP findings in pontine haemorrhage is low compared with CT or MRI. However, there are some differences between the BAEP findings in pontine haemorrhage and severe ischaemic vascular lesions of the brainstem. Loss of the whole potential, including wave I, was unusual on initial recordings in our patients with pontine haemorrhage whereas about one-quarter of the patients with basilar artery thrombosis had absent or only a flat desynchronized BAEP initially (Ferbert *et al.*, 1988). There were no major age differences between these 2 patient groups which could explain a higher degree of cochlear dysfunction in the older age group. The direct ischaemic damage to the cochlea, which is often to be found in basilar artery thrombosis, is not observed after pontine haemorrhage, even if large, at least in initial recordings. Whether the progressive loss of all waves in the course of the disease, which was occasionally observed in our patients, is due to a compression of the arteries supplying the cochlea or whether this is due to ototoxic medication or other intensive care measures, remains undetermined.

The prognostic value of the BAEP in our patients was not uniform. None of the patients with loss of all potentials after waves I and II bilaterally survived. When waves I–V were preserved with normal amplitudes, at least on one side, the prognosis was good. However, preservation of later waves with reduced amplitude could be found in patients with a poor as well as with a good prognosis. This is in contrast to experience with supratentorial lesions leading to secondary brainstem compression where a pathological BAEP reliably indicates a poor prognosis (Uziel *et al.*, 1982; Cant *et al.*, 1986; Riffel *et al.*, 1987). Uncertainties in the prognosis of these patients only arise when BAEPs are normal, which may be associated with a good as well as a bad clinical course (Anderson *et al.*, 1984; Cant *et al.*, 1986). This difference may be explained by the following. A loss of BAEP waves in secondary brainstem compression is assumed to indicate not only the destruction of the auditory pathways, but more likely a lesion of the whole brainstem at the level of the generator of the altered wave, including brainstem structures lying rostral to this level. This explains the poor prognosis of these patients. In primary medullary and pontine lesions, however, loss of BAEPs may be due to a lesion which is relatively selective to the auditory pathways, leaving other brainstem structures at the same level or in the rostral direction intact.

Two patients had only wave I of the BAEP preserved and both had preserved brainstem functions. This BAEP finding has been described as a typical finding in brain death (Starr, 1976; Mauguière *et al.*, 1982). Our results demonstrate that absence of all waves after I is not a reliable indicator of brain death in patients with pontine haemorrhage. The same has been demonstrated for severe ischaemic brainstem infarctions (Ferbert *et al.*, 1988). The same probably holds true for patients with severe brainstem lesions of different aetiology and therefore the BAEP should not be used in the diagnosis of brain death in these patients.

Delayed latency of peaks is assumed to be the main pathology of BAEP waves in demyelinating disease. In our patients reduction of amplitudes and loss of waves were the predominant findings. This has also been reported by Chiappa (1983) in a case with pontine haemorrhage.

Most of our patients had large haemorrhages and it is not possible to draw any conclusions as to the generators of single BAEP waves in these patients. Only 1 patient had a small strictly unilateral pontine haematoma as described by Kase *et al.* (1980).

This may be due to the fact that most of the recordings were carried out in the intensive care unit and thus patients with less severe syndromes may not have been included.

The patient with unilateral bleeding into the pontine tegmentum displayed a severely altered BAEP on the ipsilateral side after wave II. This is in agreement with the conclusions of Chiappa (1983) in his short survey on lateralization of BAEP waves, who assumed that 'lesions . . . of the pons primarily produce BAEP abnormalities on the same side'. However, the pathological IV/V complex after contralateral ear stimulation in our patients suggests that these waves are generated for the most part in the contralateral ascending auditory pathways, which is substantiated by anatomical studies. Another patient with bleeding predominantly on the left had the most severe alterations of waves IV–V on the right. The intracranial recordings of Hashimoto *et al.* (1981) and Møller and Janetta (1982), as well as a report of a patient with a right tegmental pontine haemorrhage and isolated loss of wave V after contralateral ear stimulation (Hashimoto, 1986) support this interpretation. Thus a lesion of the tegmentum of the lateral pontomedullary junction will possibly lead to changes in the ipsilateral BAEP after wave II. Lesions which are more rostrally located in the middle or upper pons will disturb wave V (and possibly IV) after contralateral ear stimulation. As has been explained by Maurer *et al.* (1980) and Stockard *et al.* (1986), the search for generators of waves is limited by the fact that rarefaction and condensation clicks may provide different results from the same patient. This effect was also observed in our study.

SEPs were of good prognostic value in our patients. Wherever 'cortical' SEPs (N20 and subsequent waves) were absent bilaterally, no patient recovered. Destruction of both medial lemnisci requires a large lesion. Only in the caudal pons are the medial lemnisci close to the midline, whereas they run more laterally in the middle and upper part of the pons (the term 'medial' can only be understood in relation to the location of the 'lateral' lemniscus). Thus a large lesion is required before SEPs disappear bilaterally. This explains the poor prognosis for our patients with loss of SEPs bilaterally and also why SEPs may be preserved on one side despite extension of the bleeding across the midline. The medial lemnisci must have been completely destroyed and not just compressed since the loss of SEPs was irreversible, even in patients who survived for many weeks and in whom the blood disappeared and only a minor lesion was visible on CT.

The good prognostic value of SEP is also known from patients with head trauma (Anderson *et al.*, 1984), hypoxic brain damage (Walser *et al.*, 1985) and severe brainstem stroke (Ferbert *et al.*, 1988). In one case only was bilateral absence of SEP associated with a good outcome in a patient with primary brainstem trauma (Rumpl *et al.*, 1983).

The fact that none of our 11 patients with bilateral loss of the N20 component of the SEP was brain dead underlines the fact that this finding is of no value for the diagnosis of brain death. In this respect our results are in clear contradiction to those of Belsh and Chokroverty (1987) who stated that 'absence of SEP after N13 and P13–P14 is characteristic of brain death'. Only changes *including* N13 are characteristic for brain death and this finding may develop in the further course (Buchner *et al.*, 1988). The latter authors found some dissociation of the N13 component depending on the montage chosen. While N13 of a cephalic referenced lead (C2−Fz) was reduced in amplitude shortly after brain death in some cases, the N13 peak was altered only later when using a C7 to 'jugulum' montage. N14 was always absent in brain death (Buchner *et al.*, 1988). The neurological status of our patients with absent SEPs bilaterally was not uniform. Whereas all of them had severe tetraparesis or tetraplegia, some were in coma and others had their eyes open.

The prognostic significance of unilateral loss of the median nerve SEP was ambiguous, but preserved cortical SEP may indicate a fairly good prognosis.

'Spinal' SEPs are most normal in patients with pontine haemorrhage apart from changes due to a peripheral neuropathy. Further montages of subcortical SEPs did not show a definite abnormality. Thus the recorded SEP must have been generated below the level of the pons (Buchner *et al.*, 1987).

Hemisphere functions may be nearly normal in patients with pontine bleeding. However, they can barely be assessed clinically because of the interruption of many efferent and afferent pathways. Intact function can only be demonstrated by the spontaneous EEG or by VEP recordings. The extreme form of this forebrain disconnection syndrome has been described as isolated brainstem death (Ferbert *et al.*, 1986). The progressive slowing of the EEG activity detected in our patients cannot be explained by structural changes in the forebrain hemispheres. There was no correlation with hydrocephalus. It may be the result of reduced sensory input to the forebrain or progressive loss of arousal from the reticular formation.

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RESPONSES OF LEG MUSCLES IN HUMANS DISPLACED WHILE STANDING

EFFECTS OF TYPES OF PERTURBATION AND OF POSTURAL SET

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SUMMARY

Toe-up or toe-down tilts of a platform on which a subject stands induce early EMG responses in the leg muscles initially stretched by the perturbation and late responses in the antagonist muscles. Early responses are thought to be connected with the stretch of the leg muscle in which they appear. Disagreement exists as to the origin of the late responses occurring in the antagonist muscle. The aims of this study were to assess (1) whether the late responses are induced by afferent volleys from the spindles of the muscle stretched by the initial perturbation, or (2) whether they are connected with the induced overall postural imbalance, and (3) whether the postural set may influence the occurrence of the late responses. Subjects standing on a platform underwent randomized perturbations stretching the soleus (Sol) muscle (upward tilts and backward translations) and tibialis anterior (TA) muscles (downward tilts and forward translations). The platform movement was regulated in order to yield changes in ankle angle of similar extent and velocity during both tilt and translation. Surface EMGs of Sol and TA were recorded bilaterally. An optoelectronic device detected the movements of markers fixed on the body. From these data, movements of the head, and changes in hip, knee and ankle angles, along with variations in the length of Sol, gastrocnemii (Gas) and TA were computed.

Both tilts and translations, equally stretching Sol or TA, induced similar early responses in the stretched muscle. Consistent late responses in the antagonist muscle (antagonist reactions, ARs) were induced only by tilts. In spite of similar changes in ankle angles, the most striking differences in body movements between tilts and translations stretching the same leg muscle concerned changes in knee angles and Gas length. Slight differences were also seen in vertical head movements. Standing and holding onto a frame strongly decreased the amplitude and the frequency of occurrence of both early responses and ARs only in the TA muscle, while all Sol responses were not affected. This modulation of TA responses occurred in spite of changes in ankle angle and head movements similar to those occurring under the free-standing condition. It was concluded that early EMG responses are connected with the stretch of the muscle induced by the platform movement. The ARs, on the other hand, appear to be related to the type of overall postural imbalance. The absence of ARs during translations suggests a role in these responses of the afferences from the joint and muscles of the lower limb. The data also show the relevance of the postural 'set' in the modulation of the TA responses.

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INTRODUCTION

The behaviour of the human body during normal stance has been compared with that of an inverted pendulum, swaying around the axis of the ankle joints (Gurfinkel, 1973). This unsteady equilibrium leads to a continuous acceleration of the body in a forward or backward direction. As a consequence, in order to prevent the body from falling, appropriate torques must be applied by the feet to the ground. The inertial reaction forces of the body and the viscoelastic properties of the joints and muscles of the ankles are generally enough to counteract the body sway. Postural tonic activity in the soleus muscle coöperates with the stiffness of the ankles in minimizing the body sway, while stretch reflexes play a small role in the maintenance of the upright position (Soames and Atha, 1981; Gurfinkel *et al.*, 1983).

When a standing subject is suddenly displaced by a postural perturbation, the inertial reaction force and the stiffness of the ankles are not enough to counterbalance the body sway. In this case, reflex activation of the leg muscles stretched by the perturbation counteracts the changes in ankle angle induced by the displacement and contribute in restoring equilibrium (Nashner, 1976; Allum, 1983).

The tilt of a platform on which a subject stands can induce EMG bursts not only in the leg muscle initially stretched by the perturbation, but also in the antagonist muscle (Allum and Büdingen, 1979), and a rather stereotyped sequence of events can be consistently observed. The muscle responses are usually identified according to the latency of their onset. Those appearing at a short latency seem to be connected with the muscle stretch, and have been considered to be a monosynaptic reflex. Accordingly, their amplitude and frequency of occurrence is influenced by the velocity of platform displacement (Diener *et al.*, 1984*a*). Medium-latency responses in the stretched muscle have been considered to be reflex responses relayed through polysynaptic spinal pathways, possibly mediated by impulses from group II muscle afferents (Dietz *et al.*, 1984, 1985). The mechanisms responsible for the bursts occurring at longer latencies, however, are still to be clearly identified. Long-latency responses might be mediated through long-loop pathways also travelled by the spindle discharge triggered by the same stretch (Diener *et al.*, 1984*a*; *see* Diener *et al.*, 1985), or be induced by vestibular stimulation linked with the body perturbation (Allum and Pfaltz, 1985). Compensatory reactions to forward fall might also be connected with stimulation of receptors located in the abdomen or trunk (Do *et al.*, 1988).

The issue is complicated by discrepancies in the definition of the various EMG responses between the different authors (Nashner, 1977; Allum, 1983; Diener *et al.*, 1984*a*). This, in turn, may be connected with different experimental conditions or methodological approaches. For example, forward or backward leaning of the body prior to platform displacement (Diener *et al.*, 1983), and the velocity or amplitude of platform tilt (Diener *et al.*, 1984*a*) can influence latency, amplitude or frequency of occurrence of the EMG responses. Furthermore, some authors have recorded from the soleus (Allum, 1983), some from the gastrocnemius medialis (Nashner, 1976) and some from the whole triceps surae (Diener *et al.*, 1984*a*). In addition, different laboratories have induced equilibrium perturbations either by translating the platform in a forward or backward direction, or by rotating the platform upwards or downwards. Others have induced ankle rotation and muscle stretch by letting inclined subjects fall forward after disconnecting a cable holding them in position (Do *et al.*, 1988).

These considerations prompted the present investigation, aimed at testing the effects of all four of the above-mentioned platform displacements, performed at different velocities, on the same subjects. In particular we were interested in assessing whether the late responses observed in the leg muscles of standing subjects were related either to the initial muscle stretch (i.e., triggered by the changes induced in the muscle directly stretched by the ankle rotation), or to the perturbation (i.e., related with the type of overall induced postural imbalance), or else were connected with the postural set (i.e., dependent on the subject standing freely or holding onto a solid frame). In fact, as far as postural imbalance is concerned, it has been observed by Nashner *et al.* (1979) that backward translations and upward tilts differ in the induced body sway in spite of similar muscle stretch. Therefore, if the muscle responses are triggered by the initial muscle stretch, they should not be affected by the type of body disequilibrium; on the other hand, they should be dependent, at least in part, on the type of postural perturbation if other inputs are relevant in generating the EMG responses.

In order to address this question, we performed platform displacements at a velocity able to yield stretch of a given leg muscle (soleus (Sol) during upward tilt or backward translation, and tibialis anterior (TA) during downward tilt and forward translation) to the same extent. In this way, the central nervous system (CNS) would be the target of an equal spindle afferent input from the muscle, in spite of the different body sway induced by the two kinds of perturbations.

The results, already presented in abstract form (Nardone *et al.*, 1988), show that early responses appear whenever a muscle is stretched, regardless of the mode of platform movement, whereas consistent late responses appear with tilts but not translations. In turn, the responses during tilt can change when the subject holds onto a solid frame. We have therefore concluded that occurrence of such responses is connected with the type of overall postural imbalance and postural 'set' more than with the initial stretch of the leg muscles induced by the platform.

METHODS

Experiments were performed on 7 healthy subjects (5 males and 2 females, aged 22–29 yrs), with no history of neurological disease, who gave their informed consent. They were asked to stand at ease on a movable platform (Lomazzi, Italy) with eyes open, arms folded at the waist and feet parallel, spaced 15 cm apart. Platform movements consisted in toe-up rotations (upward tilt) or toe-down rotations (downward tilt), around an axis parallel to a line passing through the ankle joints (distance between platform pivot and ankle joint ~ 19 cm). At the end of the movement the platform stopped at +3° or −3° from the initial position, respectively. These perturbations were intermingled at random with an equal number of backward and forward platform translations of 3 cm along an axis parallel to the feet. Eight to 10 trials were performed in all subjects for each type of perturbation and at 2 different velocities. Three subjects underwent at least 30 trials for each condition. The time interval between each trial varied randomly from 15 to 30 s.

In order to study the effect of postural set on the EMG responses, 3 subjects also underwent experimental sessions in which upward and downward tilts of the platform were induced at a velocity of 75 deg/s while they were holding onto a solid frame positioned in front of them.

Body movements were measured by detecting the changes in the positions of 5 infrared light-emitting diodes (LEDs) fixed on the following sites of the lateral aspect of the right lower limb: anterosuperior iliac spine, greater trochanter, head of the fibula, malleolus and fifth metatarsophalangeal joint. Two subjects underwent an experimental session in which the movement of the head was studied along with the movement of the lower limb. In this case, 1 LED was overlying the zygoma. The trajectories made by the LEDs on a sagittal plane along the anteroposterior (y axis) and vertical (z axis) directions during platform displacements were detected by an optoelectronic device (CoSTEL, LOG.IN, Rome) (Macellari, 1983), and converted analog-to-digital at a frequency of 33 Hz (for head movements a sampling rate of 100 Hz was used).

Surface EMGs of Sol and TA muscles of both legs were recorded through 'active' electrodes (Hagemann *et al.*, 1985). They consisted in solid-state devices in which integrated differential amplifers (×2000) were lodged (D.E.M., Italy). Interelectrode distance for each device was 1 cm, which assured maximal selectivity of recording and minimal 'cross-talk' between muscles (*see* De Luca and Merletti, 1988, for a recent discussion of this subject). The devices were positioned on the lower third of the leg, posteriorly (Sol), and on the upper third, anterolaterally (TA). Signals were band-pass filtered (30–500 Hz), postamplified (×5), converted analog-to-digital and fed to an Apple II computer at a sampling rate of 1 kHz. The time of acquisition was 400 ms. Platform position signals were also sampled at a frequency of 1 kHz. The changes of joint angles in the lower limb were computed from the raw data of the trajectories made by the LEDs during perturbation. All joint angles were computed with respect to the initial angle value (before displacement), which was attributed 0°. A positive increase in joint angle corresponded to extension of the hip, flexion of the knee and extension of the ankle (i.e., plantarflexion of the foot), respectively. The angular velocities of foot rotations correspond to the derivative of the trajectory of the rotation at the point of maximal slope.

The changes in length of Sol, gastrocnemii (Gas) and TA were computed by a dedicated program from the changes in position of the LEDs along the sagittal plane during movement. The position of the insertion of the Achilles tendon on the heel was assumed to be 7 cm from the malleolus, on a line forming an angle of 120° with a line joining the malleolus to the metatarsophalangeal joints. The changes in length of Gas were calculated taking into account the fact that its muscle fibres end in the Achilles tendon about 25 cm from the heel. The distal insertion of the TA muscle was on the midpoint of the line linking the malleolus to the fifth metatarsophalangeal joint. The proximal insertions of both Sol and TA were considered to be on the proximal third of the segment joining the head of the fibula and the malleolus. The proximal insertion of Gas was assumed to be on the femoral condyles at about 10 cm from the head of the fibula, on a line joining the latter with the greater trochanter.

The muscle responses were identified as follows. Short-latency responses (SLRs), evoked in the Sol muscle on stretch (upward tilt or backward translation), could consist of a burst compatible with a monosynaptic response (SLRa) and of a secondary burst which follows shortly afterwards (SLRb) (Allum and Mauritz, 1984). The earliest response occurring in TA on stretching (downward tilt or forward translation) at a latency longer than those of Sol was called medium-latency response (MLR). Longer-latency responses were usually present in the muscles antagonistic to those initially stretched by the platform movements, and were therefore called antagonist reactions (ARs).

Onset of EMG activity was measured from the stored traces by means of a cursor, which could be manually moved on the computer screen (1 pixel = 1 ms). Latency of EMG responses was assessed as the time interval between the onset of platform movement and the beginning of the burst of EMG activity (the onset of SLRb was sometimes difficult to assess with certainty, owing to the fact that this response was rather small and might occur at the end of SLRa). After digital rectification of the raw EMG signals, the areas of the EMG envelopes were computed within a chosen window. For the SLRa and SLRb, the window extended from the onset to the end of the bursts, for the MLR, up to 70 ms after its onset, and for ARs, up to 50 or 70 ms from the onset of these responses in Sol or TA muscles, respectively.

RESULTS

In the preliminary experiments, 4 subjects underwent sessions in which the changes in ankle angle were studied during platform displacements (both tilts and translations) within an ample range of imposed velocities (21, 45, 60, 75 deg/s or cm/s, respectively). Upward tilts and backward translations, or downward tilts and forward translations, appropriate to induce comparable changes in the ankle angles in all subjects, were carefully sought. This procedure allowed us to identify two velocities of platform displacement at which the angular velocities of ankle rotation, and therefore the extent of Sol or TA stretches, were similar during tilts and translations. The results of this procedure are summarized in Table 1.

Fig. 1 shows the results obtained in a representative subject during upward tilts (left column) and backward translations (right column) at low (upper panel) and high (lower panel) velocities of platform displacement. It shows that SLRs appeared in the stretched Sol during both perturbations, as expected. However, in spite of a stretch of the Sol muscle of the same extent for tilts and translations (*see* fig. 2), consistent long-latency antagonist reactions (ARs) occurred in the TA muscle in the case of tilts (left column). TA ARs of small amplitude could sometimes be observed in this subject during translations, when these were performed at a high velocity (lower panel).

Table 2 (part A) summarizes the data concerning the frequency of occurrence of the AR in all subjects under the two conditions. It shows that both at low and high velocity of ankle joint rotation the AR occurred in nearly all trials for upward tilts, but only in about one-fourth of all trials for backward translations. A very high velocity of backward translation was employed in 2 subjects in an attempt to trigger TA ARs; however, the maximum frequency of occurrence of these responses remained as low as 28.6% and 6.3% in both subjects, even when the angular velocity of the foot rotation

TABLE 1. ANGULAR VELOCITY AND AMPLITUDE OF ANKLE JOINT ROTATION AT SELECTED VELOCITIES OF PLATFORM DISPLACEMENT (MEANS ± SD FROM ALL SUBJECTS)*

Platform velocity	*Ankle joint angular velocity (deg/s)*	*Ankle joint amplitude (deg)*
Upward tilt		
21	33° 12′ ± 10° 12′	2° 36′ ± 0° 12′
60 or 75	86° 12′ ± 25° 18′	3° 48′ ± 0° 24′
Backward translation		
21	31° 42′ ± 7° 24′	2° 18′ ± 0° 18′
45 or 60	87° 24′ ± 22° 42′	3° 48′ ± 0° 24′
Downward tilt		
21	34° 06′ ± 3° 12′	3° 18′ ± 0° 12′
60 or 75	102° 42′ ± 23° 24′	3° 42′ ± 0° 18′
Forward translation		
21	30° 48′ ± 7° 18′	2° 30′ ± 0° 24′
60 or 75	100° 42′ ± 23° 36′	3° 18′ ± 0° 30′

* Platform velocity is deg/s or cm/s for tilts and translations, respectively.

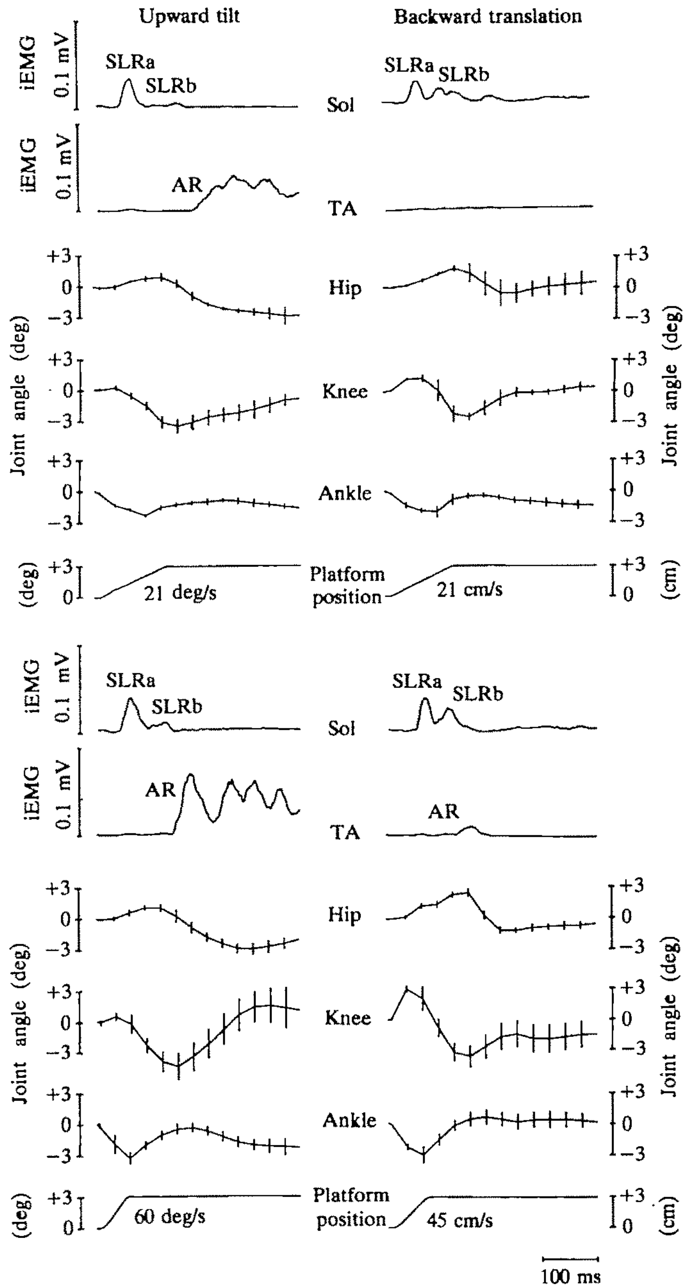

FIG. 1. Early and late EMG responses of soleus (Sol) and tibialis anterior (TA) and changes in lower limb joint angles during upward tilts and backward translations yielding equal changes in ankle angle. Upper and lower panels refer to low and high velocity of platform displacement. Positive angle values indicates extension for the hip, flexion for the knee and plantarflexion for the ankle (means ± SD of 8 trials). Short-latency responses (SLRs) appear in the stretched Sol during both upward tilts and backward translations. However, in spite of Sol stretch to the same extent in both types of perturbations, consistent TA antagonist reactions (ARs) appear only for upward tilts. Note the different behaviour of the knee joint induced by the two perturbations.

TABLE 2. FREQUENCY OF OCCURRENCE OF ANTAGONIST REACTIONS (ARs) DURING PLATFORM DISPLACEMENTS INDUCING THE CHANGES IN ANKLE ANGLE GIVEN IN TABLE 1

A Tibialis anterior AR

Platform velocity	*Upward tilt*	*Backward translation*
Low	97.5% ± 3.4	30.3% ±25.1
High	95.3% ± 4.1	24.1% ±16.1

B Soleus AR

Platform velocity	*Downward tilt*	*Forward translation*
Low	85.6% ±17.6	26.3% ±36.0
High	84.2% ±11.6	20.8% ±19.1

TABLE 3. EFFECTS OF VELOCITY OF PLATFORM DISPLACEMENT ON THE LATENCY AND AREA OF THE EARLY RESPONSES IN THE STRETCHED MUSCLE AND OF THE ANTAGONIST REACTIONS (ARs) DURING DISPLACEMENTS INDUCING THE CHANGES IN ANKLE ANGLE GIVEN IN TABLE 1

A *Perturbation stretching soleus*			B *Perturbations stretching tibialis anterior*		
EMG response	*Upward tilt*	*Backward translation*	*EMG response*	*Downward tilt*	*Forward translation*
Low velocity					
SLRa (ms)	42.3± 3.3	44.8± 3.4	MLR (ms)	86.3± 9.2	83.8± 6.4
TA AR (ms)	148.3±15.6	145.0±10.6	Sol AR (ms)	168.9±11.5	204.4± 7.0
SLRa (mV·ms)	1.0± 0.3	0.8± 0.3	MLR (mV·ms)	3.8± 1.8	5.9± 2.0
TA AR (mV·ms)	2.8± 1.1	1.4± 0.6	Sol AR (mV·ms)	2.3± 0.9	1.8± 0.5
High velocity					
SLRa (ms)	42.7± 3.1	44.3± 3.4	MLR (ms)	79.3± 7.2	80.7± 6.2
TA AR (ms)	135.2± 8.8	120.0±22.7	Sol AR (ms)	167.3±10.4	175.5± 8.5
SLRa (mV·ms)	1.5± 0.5	1.5± 0.5	MLR (mV·ms)	4.6± 1.4	5.8± 1.9
TA AR (mV·ms)	3.5± 1.5	2.0± 0.9	Sol AR (mV·ms)	2.8± 1.2	1.9± 0.8

was 103 and 110 deg/s respectively, that is, much higher than the minimum angular velocity that was required to obtain the maximum frequency of occurrence of AR during upward tilts (29 and 30 deg/s, respectively).

The latencies of the SLRs in the stretched Sol muscle were very similar in the two perturbations in all the subjects, both at low and high velocity of platform movement (Table 3, part A). When the delay of the second component of the short-latency response (SLRb) was measurable, it averaged 58.5 ±4.1 ms and 61.8 ±2.4 ms for upward tilts and backward translations, respectively (at a high velocity of platform displacement). The ARs in the TA, which occurred during upward tilts, appeared immediately at the end of the SLRb in the Sol, and persisted throughout the analysis time, showing a rather slow decrease in amplitude.

The area of the early responses in the Sol were similar in both perturbations (Table 3, rows 3 and 7). The TA ARs, on the other hand, had a smaller area during translations in respect with tilts. Rotating the ankle joint at a faster velocity induced, in all subjects, an increase in the area of all the responses.

The differences in the reactions to the two perturbations were not restricted only to EMG responses. Fig. 1 shows the changes in lower limb joint angles induced by the perturbations. The amplitude and velocity of ankle rotations were remarkably similar during the early part of tilt and translation, corresponding to the dynamic phase of platform displacements (hereafter referred to as phase I). The changes in ankle angle during the phase in which the platform was stationary (phase II), however, were different between the two perturbations, since the ankle remained in a dorsiflexed position in the tilts, while it recovered quickly towards the initial position in the translations. The knee remained more or less in its initial position in phase I of the tilts, while it was flexed in the translations (more than 3° at high velocity). The hip movements were not much different in phase I of tilt and translation. In phase II, however, the hip remained flexed during tilts, while it nearly recovered to its initial position during translations.

The differences in the changes in the lower limb joint angles, observed under the two perturbations, are mirrored in the differences observed in the length of the leg muscles under the same conditions (fig. 2, left panels). In fact, very much the same changes in the length of Sol and TA are present in the early period of upward tilts and backward translations. Instead, the behaviour of Gas differs strikingly. Under both conditions Sol was stretched and TA shortened by the perturbation, while Gas was strongly stretched during upward tilts and only transiently during backward translations. This was apparently due to the large flexion of the knee during backward translations (*see* fig. 1).

Slight differences were consistently observed in the movements of the head during upward tilts and backward translations. It is shown (fig. 3, left panels) that the head was displaced upwards during upward tilts, and downwards during backward translations, while the displacements along the anteroposterior axis were similar. These movements already occurred during the phase of platform displacement, but generally reached a consistent amplitude (4–6 mm) only some 200 ms after the onset of the displacement. The velocity of platform displacement influenced to a minor extent both the amplitude and the latency of head movements.

Fig. 4 shows the EMG and the mechanical data obtained following downward tilts of the platform (left column) and forward translations (right column), performed at low (upper panel) and high (lower panel) velocities of platform displacement. The velocities of the two pairs of perturbations were such as to induce equal changes in ankle joint angle (Table 1). Under these conditions, the earliest muscle response was a MLR, appearing in TA, which was initially stretched by both perturbations. During tilts, the MLRs were usually short and subsided at the time when a small AR appeared in Sol. During translations, the TA burst was longer and was followed by tonic activity of a smaller amplitude lasting throughout the analysis time. In spite of the similarities in the changes at the ankle joint, ARs were consistently observable only for downward tilts, while they occasionally appeared with forward translations performed at very high velocities. The frequency of occurrence of the ARs was again higher for tilts than for translations (*see* Table 2, part B).

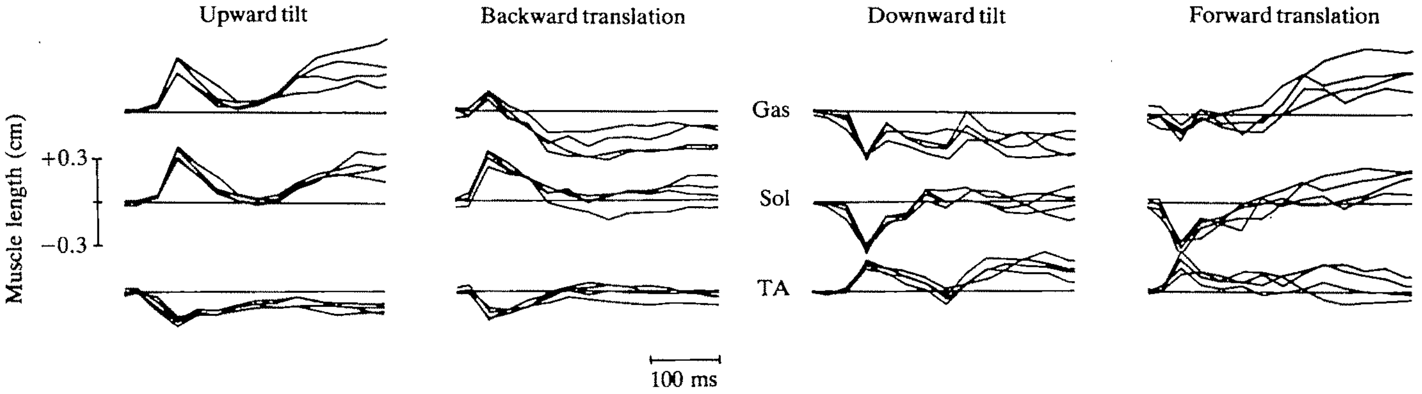

FIG. 2. Effects of perturbations stretching Sol (*left panels*) and TA (*right panels*) on changes in length of Gas, Sol and TA muscles (same subject as in fig. 1). Superimposition of 4 random trials at high velocity of platform displacement. In spite of similar changes in length of Sol and TA between perturbations stretching the same muscle, the changes in length of Gas differ strikingly.

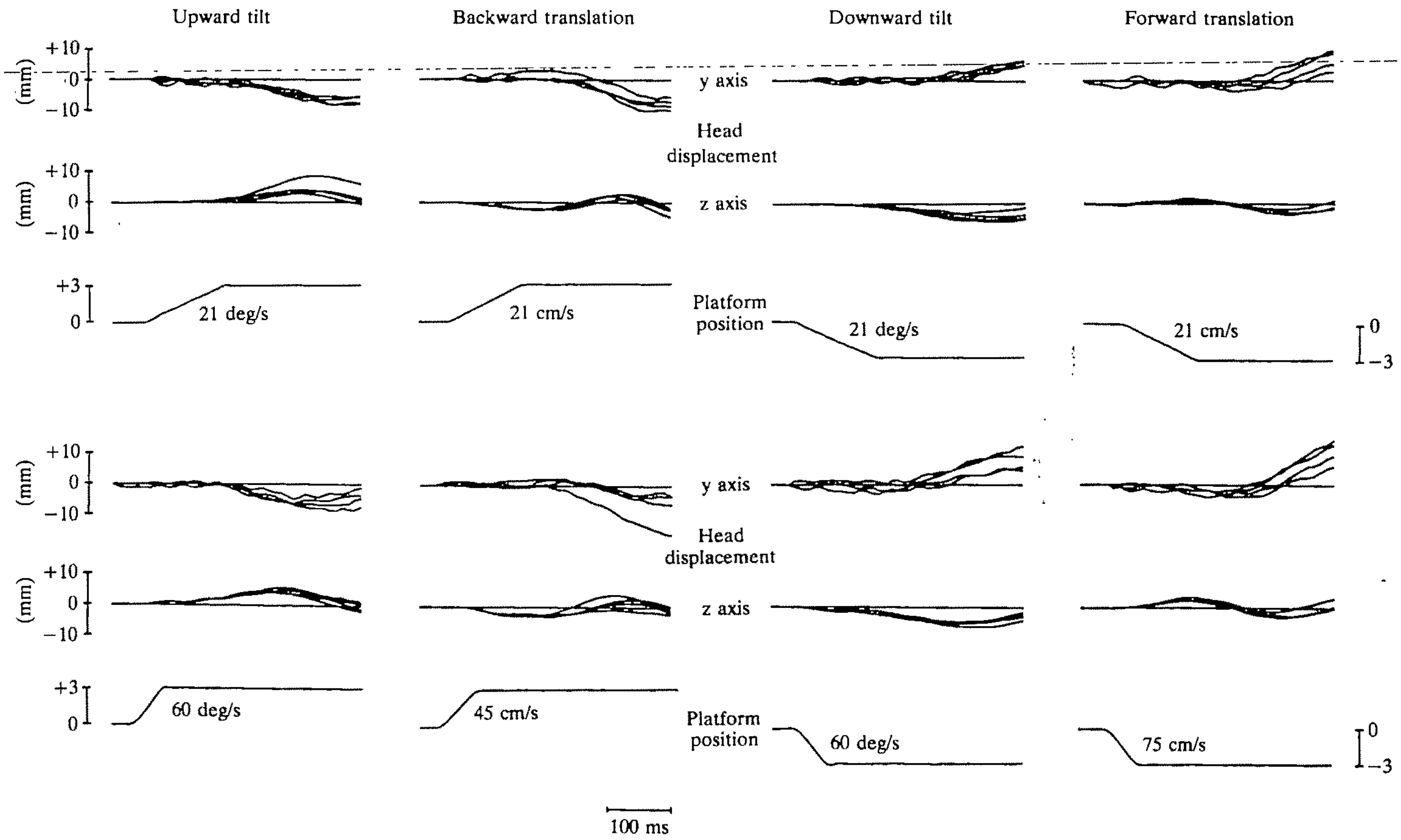

FIG. 3. Changes in head position during perturbations stretching Sol (*left panels*) and TA (*right panels*) performed at low (*upper panels*) and high velocity (*lower panels*) of platform displacement. Superimposition of 4 random trials. Upward deflections of the traces in the y and z axes correspond to backward and upward displacements of the head, respectively. Vertical calibration of platform displacements is deg or cm for tilts and translations, respectively. Vertical changes in head position are different between perturbations stretching the same leg muscle (compare z axis within the left and right panels). However, they are not specific for each type of perturbation, since similar movements are induced by perturbations stretching either Sol or TA (compare upward tilts with forward translations, and backward translations with downward tilts).

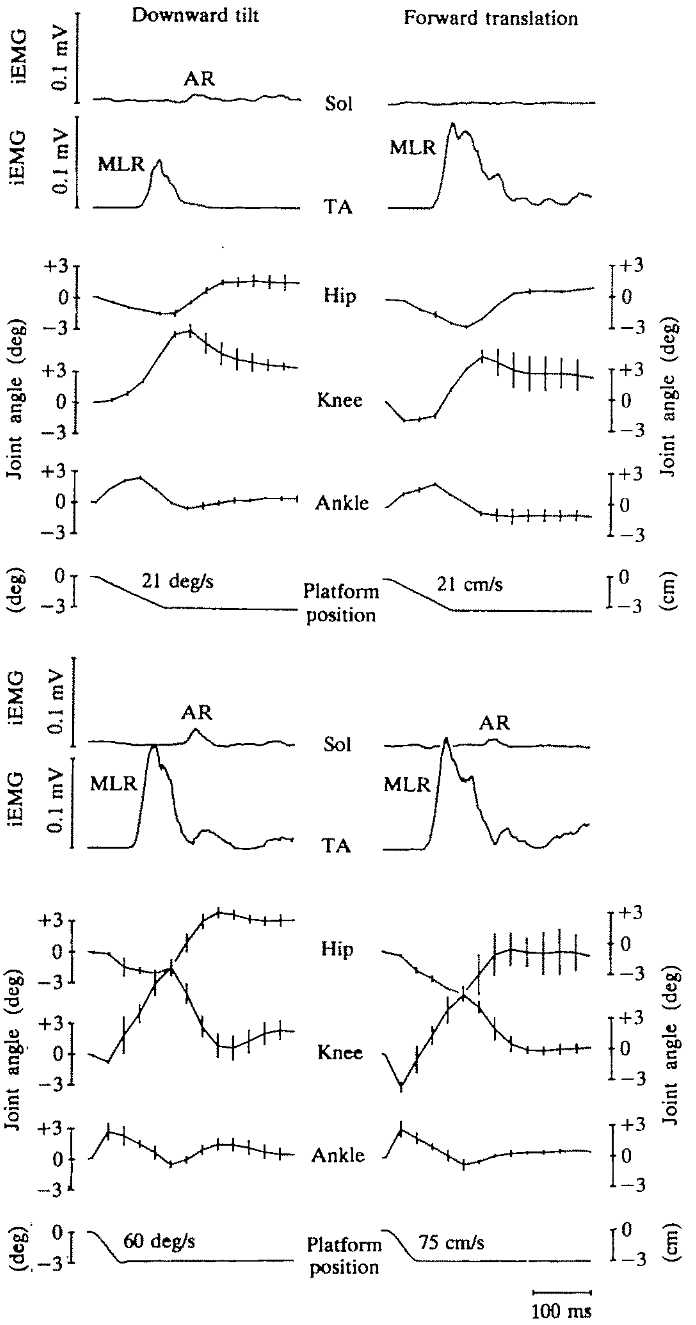

FIG. 4. Effects of velocity of platform displacement on early and late responses of Sol and TA and on changes in lower limb joint angles during downward tilts and forward translations, when the induced changes in ankle angle are similar. Same labelling as in fig. 1. Medium-latency responses (MLRs) appear in the stretched TA in both perturbations. During downward tilts, the MLR usually subsides when a small AR appears in the Sol. In spite of the similarities in the changes in ankle joint, ARs are consistently observable only for downward tilts. The two perturbations greatly differ in the induced changes in knee angle.

The latencies of the TA MLRs were very similar in both perturbations (Table 3, part B). The latencies of ARs in the Sol muscle were somewhat different under the two conditions, being longer for forward translations. The area of the TA MLRs was generally greater for translations than for tilts. Increasing the angular velocity of the ankle induced a slight and inconstant increase in the area of both MLRs and ARs.

Also, for downward tilts and forward translations, differences were seen in the movements of the lower limbs (fig. 4). While both perturbations induced initially (phase I) a plantarflexion of a similar extent, the ankle joint remained slightly plantarflexed (tilts) or dorsiflexed (translations) during the following stationary phase (phase II). The knee angle changed only slightly during phase I of downward tilts. On the other hand, the knee was strongly extended during phase I of forward translations. During phase II the knee was considerably flexed under both tilts and translations. The hip, flexed during both perturbations in phase I, was hyperextended during tilts, overshooting the initial position, while it returned to the initial placement during translations.

As was the case for the perturbations that stretched the Sol, the two perturbations stretching the TA again induced clear-cut differences in the length of the leg muscles and in limb joint angles (fig. 2, right panels). Whereas Sol and TA underwent equal changes in length during the early period of both downward tilts and forward translations (TA was stretched and Sol was shortened), Gas was shortened strongly during downward tilts, but only transiently and to a lesser extent during forward translations. This was apparently due to the marked extension of the knee during the early part of forward translations (*see* fig. 4).

Head movements were slightly different during downward tilts and forward translations (fig. 3, right panels) as far as the movements along the z axis were concerned. The head moved downwards during downward tilts, and upwards during forward translations. Again, these changes began during the phase of platform displacement, and the largest movements were observed during the following motionless phase. Increasing the velocity of displacement induced a slight decrease in the latency and an increase in the amplitude of the head movements.

The influence of the 'postural set' was studied in 2 subjects, who also participated in the sessions described already. They were asked to stand on the platform while holding onto a frame placed in front of them. They were subjected to upward and downward tilts, at high velocity of platform rotation, sufficient to induce consistent ARs in the leg muscles while standing freely. It was carefully checked that before the perturbation no changes in the body position occurred in respect to the free-standing condition.

The results from 1 subject are shown in fig. 5. Sol displayed the SLRa during upwards tilts, and AR during downward tilts, as in the free-standing conditions. TA, contrary to Sol, did not show either the MLR when initially stretched (downward tilts), or the AR when the stretched muscle was Sol (upward tilts).

These differences in the EMG responses of the stabilized subjects, with respect to the free-standing conditions, took place even if the changes in the ankle joint angles induced by the two types of perturbation were substantially similar under the two conditions. This is true as far as the displacements occurring during tilts and the first

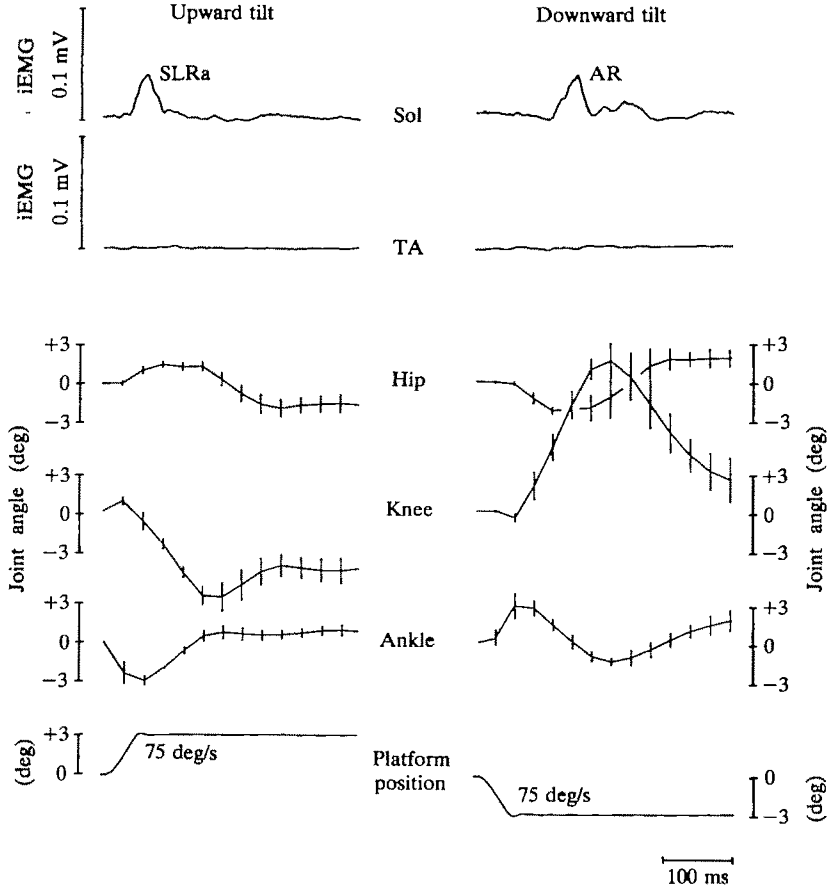

Fig. 5. Effects of holding onto a frame on the EMG responses of leg muscles and on the changes in lower limb joint angles during upward and downward tilts, performed at high velocities of platform rotations (same subject as in the preceding figs). Labelling as in fig. 1. Sol shows both the SLRs during upward tilts and the ARs during downward tilts. TA does not show either the MLRs during downward tilts or the ARs during upward tilts, in spite of initial changes in ankle angles similar to those occurring under the standing freely condition.

part of the motionless period are concerned. In fact, towards the last part of the analysis time, the changes in joint angles while being stabilized were very different from those occurring under the free-standing condition. The low and incomplete return towards the initial position of the knee joint, which characterizes upward tilt under the stabilized condition (fig. 5), is most probably connected to the absence of active restoring forces in TA.

Fig. 6 shows that the initial changes in muscle length are similar to those occurring during the same perturbations performed under the free-standing condition (*cf.* fig. 2). The changes that occurred in the later part of the perturbations were no longer equal to those observed under the corresponding free-standing conditions. This is probably connected with the absence of the TA early and late EMG responses.

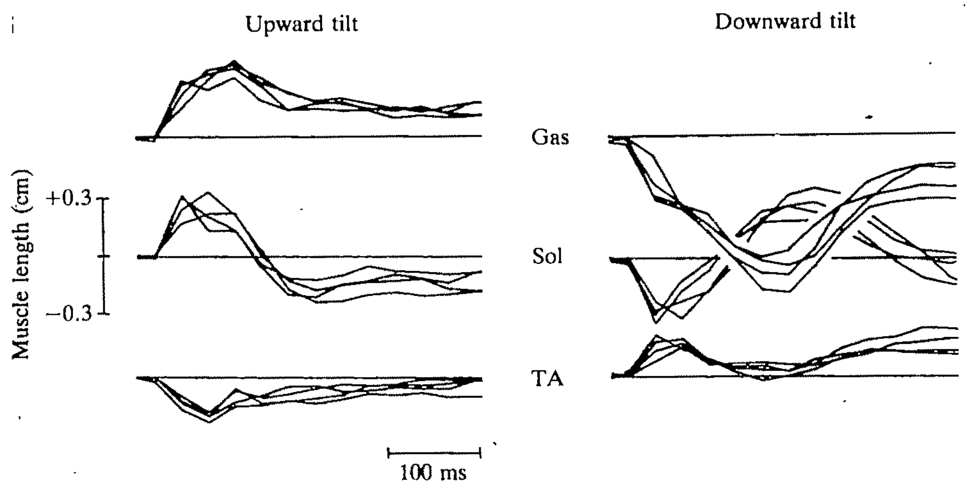

FIG. 6. Effects of holding onto a frame on the changes in muscle length of Gas, Sol and TA during upward and downward tilts. Labelling as in fig. 2. The initial changes in muscle length are similar to those occurring during the same perturbations performed under the standing freely condition.

No obvious changes in head movement were observed during upward and downward tilts while being stabilized in comparison with those occurring under the respective free-standing condition (fig. 7).

DISCUSSION

Different displacements of a platform on which a subject stands, able to stretch a given leg muscle to a similar extent and velocity, induce different body sways. In spite of this, the early responses evoked in the stretched muscle (Sol during upward tilts and backward translations, or TA during downward tilts and forward translations) are equal. A clear difference, however, is present in the antagonist muscle reactions (ARs): in fact, during tilts and translations stretching the same leg muscles, ARs appear consistently during tilts, while an almost systematic lack of ARs can be observed for platform translations. Keshner *et al.* (1988) also examined EMG responses to tilts and translations, but in their experimental procedure changes in ankle angle were very different between the perturbations stretching the same leg muscles. Under those conditions, variations in the pattern of EMG activity could be ascribed to an unequal afferent input from the stretched leg muscles. In our experiments care was taken to perform platform movements such as to yield similar changes in length of the leg muscles during both tilts and translations stretching Sol or TA, in order to obtain an equal input to the CNS from the spindles of the stretched muscles. If the ARs were evoked in an all-or-none fashion by the initial stretch of the leg muscles (Diener *et al.*, 1984*a*), they would occur during both tilts and translations. The present results seem to indicate that, while the occurrence of the early responses is connected with the initial muscle stretch, the ARs are strongly influenced by the type of postural imbalance induced by the perturbations, and by the postural set.

Early responses occurred in the stretched leg muscles, whatever the type of induced body sway. The responses could be divided into two groups on the basis of the latency: those occurring at a delay compatible with a monosynaptic reflex, such a Sol SLRa, and those occurring later, such as Sol SLRb and TA MLR. As far as the Sol SLRa is concerned, little doubt exists that it is mediated by a stretch reflex, through a monosynaptic or oligosynaptic pathway (Jankowska *et al.*, 1981): it is a rather synchronized EMG burst, with a constant latency of about 42 ms after the onset of platform movement. Our results confirm previous observations that increasing the velocity of platform displacement induces an increase in the area of SLRa (Gottlieb and Agarwal, 1979), but not a decrease in the latency of the response (Diener *et al.*, 1984*a*). Also, Sol SLRb and TA MLR might be related to the stretch of the same muscle in which they appear. In fact, Sol SLRb occurs at similar latencies during both upward tilts and backward translations, and TA MLR occurs at similar latencies during both downward tilts and forward translations. The longer latency of these responses could be explained by the fact that they may be fed by group II fibres and travel through a polysynaptic spinal pathway (Dietz *et al.*, 1984, 1985). Alternatively, Sol SLRb and TA MLR could be long-loop reflexes evoked by the Ia discharge. The connection of these responses with the initial stretch of the leg muscles is also suggested by the fact that the faster the velocity of ankle rotation the larger the area and the shorter the latency of the responses (*see also* Diener *et al.*, 1984*a*, 1988).

It must also be considered whether other afferents, which are put into play by the movements of the body, may trigger the TA MLR and Sol SLRb. In this regard, it is unlikely that other proprioceptive cues from proximal muscles or joints may trigger these responses. It has already been shown by Bussel *et al.* (1980) that proprioceptive inputs from proximal muscles of the lower limb can modulate the amplitude, but not the latency, of early EMG responses of leg muscles induced by a perturbation. It has also been shown that the afferent input from the sole of the foot, which might be somewhat different during tilts and translations, plays no role in evoking early responses (Diener *et al.*, 1984*b*). It has recently been suggested that early responses could be connected with stimulation of receptors located in the abdominal wall (Do *et al.*, 1988). This does not seem to apply in our experiments, because perturbations stretching to an equal extent the same leg muscles and yielding similar EMG responses induce different body movements, and therefore different input from the abdomen. Neither do vestibular afferents appear likely to trigger the early responses: in fact, just before the occurrence of these responses, head movements are very small and, additionally, differ between perturbations stretching the same muscle. Finally, it seems unlikely that these responses represent a 'startle' reaction to the perturbation, since this reaction would appear as a constant EMG response in the same muscle in all the trials, independent of the muscle initially stretched by the perturbation.

The late responses (ARs) occurring in the muscles antagonistic to those initially stretched can be considered the true compensatory responses to the disequilibrium (Diener *et al.*, 1984*a*). They must arise reflexly in the CNS since no cue was given in advance to the subjects, and the perturbations were delivered in a random and completely unpredictable manner (Keshner *et al.*, 1987). The questions raised by these results include the frequency of the occurrence of ARs, their temporal characteristics within a given type of perturbation, and their strikingly unequal distribution between tilts and translations.

In the search for a stimulus adequate to evoke these responses, we used both low and high velocities of platform displacement in order to assess whether the frequency of occurrence of the ARs could be dependent on the characteristics of the initial muscle stretch. Generally, the ARs appeared with their maximum frequency even at the lowest velocities of tilts employed in this study: conversely, when the frequency was very low, such as during translations, it was hardly modifiable by changes in the velocity of perturbation. However, the velocity of platform movement affected the characteristics of the ARs. In conformity with results obtained by Diener *et al.* (1984*a*), we found an increase in the area and a decrease in the latency of the TA and the Sol ARs, related to the increase in the velocity of platform displacement. This finding might suggest that the gain of the ARs is modulated by the velocity of platform displacements and therefore by the initial stretch of the leg muscles.

The question of the very inconstant presence of the ARs during translations deserves some comment. Looking at the mechanical events occurring in the body during the different perturbations stretching the same leg muscle, it appears that in spite of changes in ankle angle of similar extent, the most striking differences are shown by the knee angle at the onset of platform displacement. It is therefore conceivable that either the output from the knee joint and the variations in Gas length (and also the changes in length of thigh muscles acting on the knee) are relevant in determining the observed ARs. This phenomenon is not surprising since it is known that proprioceptive afferents from spindles and tendon organs of lower limb muscles diverge onto homonymous and heteronymous motoneuronal pools acting at the same or at different joints (Pierrot-Deseilligny *et al.*, 1981; Mao *et al.*, 1984).

It has been suggested (Allum and Pfaltz, 1985) that vestibular afferents play an important role in triggering the ARs. Our results show that the head movements induced by the two types of perturbations stretching the same leg muscle are indeed different, at least along the vertical axis, since no early head movements along the anteroposterior axis appear to be connected with the perturbations. On the other hand, the vertical head movements are very similar between perturbations inducing clearly different EMG responses in the leg muscles (as in upward tilts and forward translations, and in downward tilts and backward translations). In addition, EMG responses in the neck muscles, induced by the various types of perturbation, also appear not to be related to the EMG of the leg muscles (Keshner *et al.*, 1988). Therefore, we believe that vestibular afferents are not appropriate for triggering the ARs. This is also suggested by the findings of Allum and Pfaltz (1985). In fact, they found that in patients with chronic vestibular disease there is a decrease only in the amplitude, but not a delay or a lack of the TA AR. The possibility that vestibular afferents play a role in triggering the ARs is also countermanded by experiments in which the displacements were performed while the subject maintained the head in various positions (Diener *et al.*, 1986). In fact, under these conditions, in spite of conceivably different afferent inputs from the labyrinths, the latency and area of the ARs were similar to those obtained with the head in a normal position.

When perturbations apt to induce large responses in the leg muscles were performed on a subject holding onto a solid frame, a marked rearrangement of the muscle responses was observed, in spite of changes in initial muscle stretch and head movements quite similar to those occurring under the free-standing condition. The EMG changes were reflected in both the TA MLRs and ARs. Interestingly, only Sol maintained the main characteristics of its responses. These phenomena appear to be connected with a change in the level of excitability of the spinal circuits due to the new postural 'set'. The changes in TA responses under the stabilized condition do not appear to be induced by a change in neuronal excitability simply caused by backward or forward leaning of the body (Diener *et al.*, 1983), due to the posture assumed while holding the frame. In fact, it was carefully checked during the experiments that ankle angles were similar under both free-standing and holding conditions. The prevalent influence of postural 'set' on the TA responses is not surprising, as it has already been shown by Gottlieb and Agarwal (1979) that in seated subjects stretch-evoked responses of TA muscle are far more influenced by prior instruction given to the subject, compared with the stretch-evoked responses in Sol, presumably because the central 'setting' may influence polysynaptic responses more than monosynaptic ones. Cordo and Nashner (1982) also found that holding while standing can reduce the TA MLR. The finding that postural 'set' influences both TA MLRs and ARs suggests that the latter responses could also be relayed through polysynaptic pathways, whose gain can be differently modulated by the postural requirements. Both TA MLRs and ARs can be considered as stabilizing responses which can be triggered by the appropriate perturbation, when they are helpful in restoring equilibrium. As a consequence, both disappear when the subject is holding, as happens under similar conditions in another postural perturbing condition, namely during voluntary contraction of triceps surae while standing (Nardone and Schieppati, 1988).

The Sol and TA ARs may well be connected with inputs from the muscles initially stretched by the perturbations. Their full expression, however, appears to be the consequence of the algebraic sum at the motoneuronal level of the discharge from the spindle afferent input with other inhibitory influences. The latter may be either a descending input from higher centres or an input from the periphery induced by the platform movement, and originating from other body structures put in motion by the perturbation. Therefore, absence of ARs during translations while free-standing, or during tilts while holding, can be due either to an inhibition from the periphery or a dysfacilitation, or both, as when the postural 'set' becomes useless in the stabilized condition.

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THREE-DIMENSIONAL COMPUTERGRAPHIC ANALYSIS OF APRAXIA

NEURAL REPRESENTATIONS OF LEARNED MOVEMENT

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SUMMARY

The left cerebral hemisphere in man contains anatomical structures specialized not only for language but also for higher-order motor programming. One method of studying the nature of these motor programs is by observing the type of errors made by patients who have left hemisphere damage. A major problem, however, in investigating the disorders that result from failure of this specialized left hemisphere system (the apraxias) has been the difficulty in obtaining objective measurement of movement in three-dimensional space. To this end, we provide the first three-dimensional analysis of the nature of movement errors in apraxia. Two apraxic subjects with lesions to the left hemisphere and 5 matched control subjects were studied. The apraxic subjects showed impairments in the control of movement timing and spatial relations, as well as decoupling in the normally tight relation between certain spatial and temporal aspects of their movement trajectories. Further, the use of the distal musculature by apraxic subjects was more impaired than their use of the proximal musculature, suggesting more distal representation in any space-time maps of learned movement. These data provide further insight into the nature of the representations of learned skilled movements in the left cerebral hemisphere.

INTRODUCTION

Ideomotor apraxia is a disorder of the execution of movement that can be accounted for neither by weakness, incoordination, or sensory loss, nor by poor language comprehension or inattention to commands (Geschwind, 1965, 1975). As such, its study promises to illuminate the organization of the motor system at the highest level. Geschwind (1965) proposed that (visual) imitation of gestures or the following of (auditory) verbal commands are first processed in their respective receptive areas, and then messages are relayed to the motor association area of the left frontal lobe via the arcuate fasciculus. The left motor association area is connected to that on the right via the corpus callosum, and each motor association area is connected to the primary motor area on the same side, which in turn effects movement of the opposite limbs. Lesions that destroy the left motor association cortex (premotor areas) and/or the anterior portion of the corpus callosum would 'disconnect' the right premotor and motor areas from the left hemisphere, which would result in apraxia of the left hand. A problem with Geschwind's

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(1965) schema, however, is that patients with parietal lesions (or arcuate fasciculus lesions) that spare motor association cortex should theoretically be able to imitate gestures, but cannot. To explain this discrepancy, Geschwind (1965) had to assume that the arcuate fasciculus of the left hemisphere is dominant for visuomotor connections. However, even if it is assumed that the left arcuate fasciculus is dominant for visuomotor connections and interruption of this dominant pathway explains why patients cannot imitate, it could not explain why these patients are clumsy when they use objects or perform other somaesthetic motor tasks. It would have to be assumed that the arcuate fasiculus also carries somaesthetic-motor impulses and that the left arcuate fasciculus is also dominant for this function. An alternate hypothesis that may explain why patients with parietal lesions cannot imitate or use an object is that spatiotemporal representations of skilled motor acts are stored in the dominant parietal cortex (Heilman, 1979). These stored spatiotemporal representations help to program the motor association cortex for the necessary movements. In order to perform a skilled motor act, particular body parts must be placed in certain spatial positions in a specific order at specific times. The spatial positions assumed by the relevant body parts depend not only on the nature of the act but also on the position and size of an external object with which the body parts must interact if such an external object is present. Skilled acts also require orderly changes in the spatial positions of the body parts with time. These spatiotemporal movement representations direct the motor systems to adopt the appropriate spatial positions of the relevant body parts over time (Heilman, 1979; Heilman and Rothi, 1985). Lesions of the corpus callosum or of the left motor association cortex therefore separate these spatiotemporal movement representations in the left hemisphere from the motor areas in the right hemisphere, producing apraxia of the left hand. Lesions of the left parietal lobe may destroy the spatiotemporal representations and also cause apraxia. The nature of this left hemisphere movement control system, however, has remained relatively unexplored. This situation has resulted in large part from the difficulty of measuring and analysing movement in three-dimensional space. It is impossible to discern precise patterns of timing and spatial relations in three-dimensional trajectories from direct observation, or from viewing videotaped recordings. However, such precise information regarding temporal and spatial trajectory variables is essential for discovering the nature of spatial-temporal representations of purposive, skilled movement. The problem of measuring and analysing movement in three-dimensional space has recently been solved, and in the present study we describe the application of these methods to the analysis of apraxia. By investigating how the brain acts when spatiotemporal representations of learned movements are damaged, we illuminate what parameters of movement the left hemisphere controls.

SUBJECTS

Case 1

B.H. is a 47-yr-old right-handed male who was admitted to hospital with an abrupt onset of aphasia. His pertinent past medical history included coronary artery bypass surgery 27 months before aphasia onset.

On examination, he had severe impairment of language function with little or no language output and very poor comprehension. He was originally diagnosed as having severe global aphasia and mild dysarthria. At that time no significant limb or oral apraxia was noted. There was a right supranuclear facial palsy and mild weakness of the right extremities. The remainder of his examination was normal.

Shortly after his admission to hospital, the patient developed a rapidly progressive right hemiplegia despite anticoagulation therapy with heparin. A CT scan indicated no evidence of haemorrhage but showed a large area of infarction. The patient's hospital course was marked by continued severe neurological deficits; he could not move his right arm or leg and was globally aphasic. He was then transferred to a rehabilitation centre for continued rehabilitation. B.H. received treatment there for approximately 2 months. At the time of evaluation at the Gainesville VA Medical Center, he was 5 months postonset and diagnosed as having severe Broca's aphasia. The tests reported in this paper were performed 16 months postonset. An MRI scan performed more than 3 yrs after his stroke indicated a large perisylvian lesion involving the frontal, temporal, and parietal lobes.

Case 2

E.T. is a 69-yr-old right-handed male who was admitted to hospital after the sudden onset of a right hemiparesis along with global aphasia. Twelve days postonset he was transferred to the Gainesville VAMC from another hospital for intense rehabilitation. At that time neurological examination showed that he was alert and orientated. His spontaneous speech was nonfluent and agrammatic, with perseverations and literal paraphasic errors. Auditory comprehension and naming were better than spontaneous speech and repetition. The results of testing were consistent with a diagnosis of Broca's aphasia. Reading tests revealed deep dyslexia. He had a right hemiparesis, the lower extremity being worse than the upper, and decreased fine motor coordination on the right. Sensory examination revealed decreased proprioception and stereognosis of the right hemibody.

A CT scan performed on admission showed a small previous infarction in the left temporoparietal region. Five months postonset, a repeat CT scan revealed a large left hemisphere lesion involving the anterior portion of the superior temporal gyrus, the lower half of the motor and sensory strips and premotor cortex. It also extended into the corona radiata as far as the lateral border of the putamen, but did not appear to affect any of the subcortical nuclei. The tests reported here were performed 1 month postonset.

Neuropsychological assessment

To obtain measures of praxis ability in both patients, the Florida Praxis Screening Test was administered. This screening tool consists of 15 gestures to be produced both spontaneously and imitatively, using the nonparetic left arm and hand. Comprehension of these same gestures was also tested. Results of screening revealed E.T. to be severely apraxic. Spontaneously, he was only able to correctly produce 1 out of 15 gestures. On the imitation task, he was only able to correctly produce 6 out of 15 gestures. Results of screening revealed B.H. to be only mildly apraxic. He was able to correctly produce 10 out of 15 gestures spontaneously and 13 out of 15 imitatively.

Control subjects

Five neurologically intact subjects, matched for age and sex with the apraxic subjects, served as control subjects. Informed consent was obtained for all subjects. All subjects were right-handed.

METHODS

Procedure

Four gestures of the type traditionally used to test for apraxia were selected for three-dimensional movement analysis: roll up a car window (WIND), erase a blackboard (ERASE), carve a turkey (CARVE), and unlock a door (KEY). These gestures were chosen because the movements involved joints not in the hand. Such movements often present the greatest difficulty for observer judgement, since their timing and spatial characteristics are crucially important but difficult to judge accurately. To minimize cues, subjects were asked to produce each gesture to verbal command, without the tool (e.g., knife) or object of the tool's action (e.g., turkey) being present. To obtain measures of movement variability, each gesture was replicated four times. All subjects performed the movements with their nondominant left hand. The subjects' left hand was used since it was ipsilateral to the side of the lesion for the brain-damaged subjects, and thus would not be affected by weakness or incoordination due to primary motor deficit.

Three-dimensional data acquisition

Two optoelectronic cameras that sense the positions of infrared emitting diodes directly were used to digitize movement trajectories (Poizner *et al.*, 1986). Infrared emitting diodes were strapped to the hand, wrist, elbow, and shoulder of the subject. Under computer control, the diodes were flashed sequentially. Only one diode was illuminated at any given point in time, providing unique joint identification, with the diodes cycled through rapidly, producing good temporal resolution. The camera signals were digitized to 12-bit (1 part in 4096) resolution by the microcomputer, which synchronized the flashing of the diodes with the digitizing of the camera signals (*see* Poizner *et al.*, 1986). The position of each of the four joints of the arm was sampled at 100 Hz. Two optoelectronic cameras were used to digitize the movements from neighbouring viewpoints so that three-dimensional coordinates could be calculated (*see* fig. 1.).

Digital data processing

The data from each camera were first corrected for lens and electronic distortion by making use of a prior calibration procedure that involved the exhaustive placement of target diodes at known locations across the field of view of each camera. In order to remove high-frequency noise, the data from each camera were low-pass filtered with a modified Butterworth filter using a cut-off frequency of 8 Hz. The three-dimensional coordinates of each joint were then calculated from the two cameras by triangulation, using knowledge of relative camera position and orientation. Finally, the three-dimensional coordinates were differentiated twice for calculation of the tangential velocity and acceleration of each joint of the arm over time.

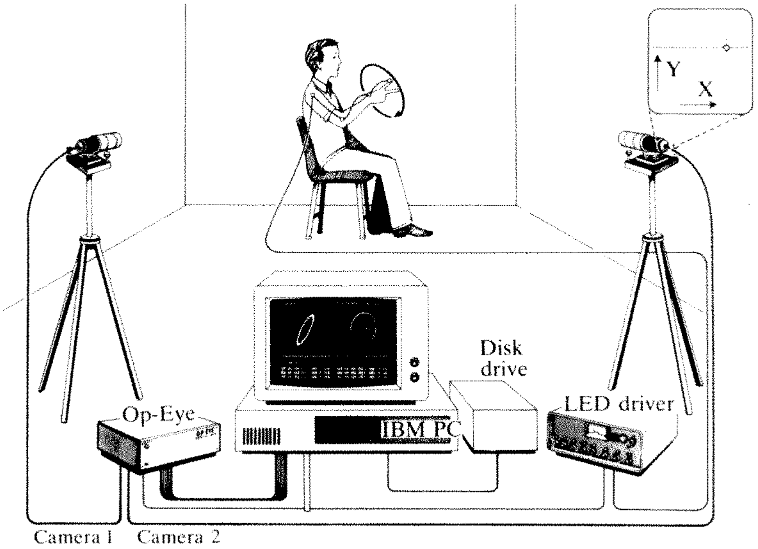


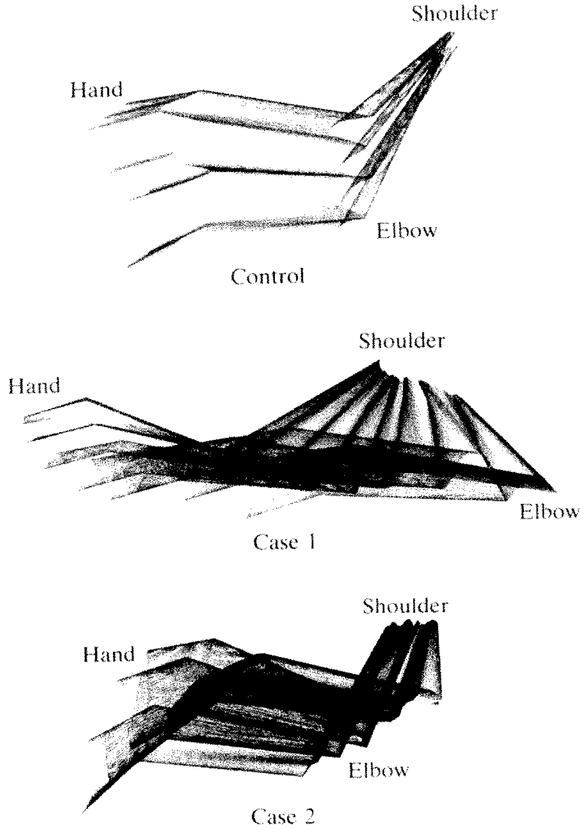
FIG. 1. Three-dimensional data acquisition system. Main hardware components and the positioning of light-emitting diodes (LEDs) on a subject are shown.

Computergraphic reconstruction

The trajectories were reconstructed in three dimensions on a computergraphics system. This system allows interactive manipulation and dynamic display of the reconstructed movement in three dimensions, including real-time rotation, translation, scaling, and clipping. The interactive control and three-dimensional visualization of the digitized movements allow separate analyses of various temporal and spatial characteristics of segments of the movement trajectory (Jennings and Poizner, 1988). All trajectories were edited graphically to remove extraneous portions at the beginning and ending of the movement related to the subject raising his hand to the initial position and dropping his hand after the movement was completed. Furthermore, since several of the gestures involved rhythmic movement repetition (e.g. WIND, ERASE, and CARVE), movements were segmented into individual repetition cycles.

RESULTS

The apraxic subjects showed clear impairment in four aspects of their control of movement: spatial orientation, distal joint control, movement initiation and timing, and space-time relations.



Control

Case 1

Case 2

FIG. 2. Three-dimensional reconstruction of the motions of the arm of a control subject and the 2 apraxic subjects performing the gesture CARVE. The entire sequence of hand and arm positions during the course of the movement is shown. Note the impaired orientation of the movement axis in the apraxic subjects.

Spatial errors

Impairments in spatial orientation of movement. The use of improper spatial orientation is evident in the reconstructed motions of the arm for a control subject and the 2 apraxic subjects performing the gesture CARVE (fig. 2). The images show the sequential positions of the arm and hand in three-dimensional space during the course of the movement. Fig. 2 clearly shows that apraxic subjects had impaired control of the direction of the movement axis. Whereas the control subject orientates the movement in the sagittal plane, both apraxic subjects orientate the movement laterally, in the transverse plane.

To capture the spatial orientation of the plane of motion and changes in that orientation during the movement, the best-fitting plane of motion of the hand trajectory for CARVE was computed for both apraxic subjects and all control subjects. This best-fitting plane of motion was computed for each replication of the gesture and for each movement repetition cycle within a given gesture. To specify the orientation of the plane in three-dimensional space quantitatively, the direction perpendicular to each plane was calculated. These directional vectors for each movement replication and repetition cycle are presented in fig. 3 (direction vectors for the control subjects are displayed in the top panel while the bottom panel presents those of the 2 apraxic subjects).

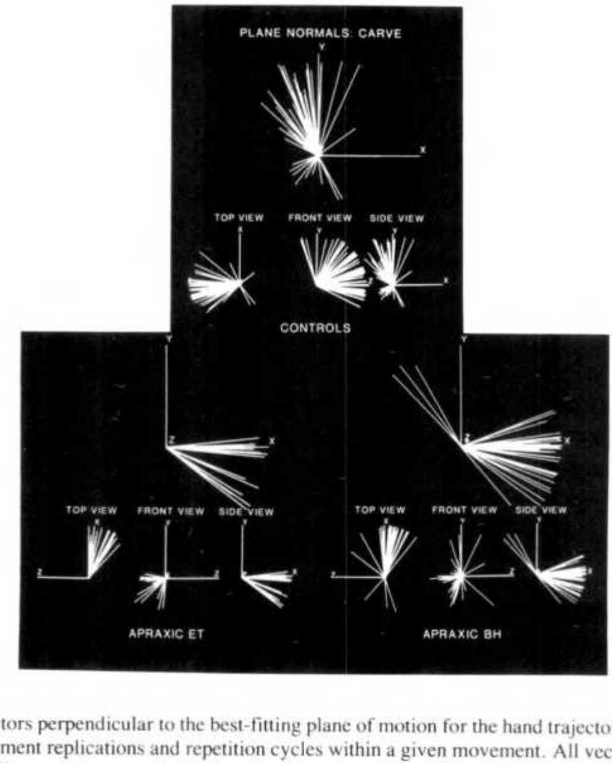


FIG. 3. Direction vectors perpendicular to the best-fitting plane of motion for the hand trajectory in the gesture CARVE are shown across movement replications and repetition cycles within a given movement. All vectors have been converted to a unit length of 1. These vectors concisely describe the orientation of the plane of motion and show the disruption in the control of planar orientation in the apraxic subjects.

To display the three-dimensional structure, the vectors are shown from four views: an enlarged side view, and smaller views from the top, front, and side of the motion. Fig. 3 shows that the control subjects have components of vectors perpendicular to the plane of motion predominantly in the frontal plane, reflecting sagittal movement. The spread of vectors seen from the top reflects a downward component of the movements. Both the apraxic subjects, in contrast, have major vector components reflecting lateral and downward movement, as seen from the side and top, as opposed to sagittal and downward movement. The sagittal and lateral components of the movement differed statistically between the control subjects and each apraxic [$t(28) = 10.6$, $P < 0.001$ for sagittal component; and $t(28) = 11.3$, $P < 0.001$ for lateral component of Case 1 versus the control subjects; $t(13) = 14.4$, $P < 0.001$ for sagittal component, and $t(13) = 11.2$, $P < 0.001$ for lateral component of Case 2 versus the control subjects]. Likewise, the orientation of the plane of motion differed between the apraxic subjects and the control subjects for the gesture ERASE. The motions of the apraxic subjects were not as tightly confined to the frontal plane as those of the control subjects. The sagittal and lateral components of the movement again differed statistically between the control subjects and the apraxic subjects [$t(101) = 5.2$, $P < 0.001$ for the sagittal component, and $t(101) = 2.9$, $P < 0.01$ for the lateral component of the control subjects versus the apraxic subjects].

Thus control over the direction of the movement axis seems impaired in apraxia. This impaired movement control is also reflected in the inappropriate addition of movement axes by the apraxic subjects. For example, fig. 4 presents the reconstructed movement of a control subject and of Case 1 for the gesture WIND. The control subject shows smooth circular movement repeated about a well-defined centre point. In contrast to the control subject, Case 1 adds a downward movement axis to his repeated circular motions. Each movement repetition cycle seems to be made about a centre point, but, unlike those of the control subject, those centre points are displaced linearly downwards throughout the course of the movement.

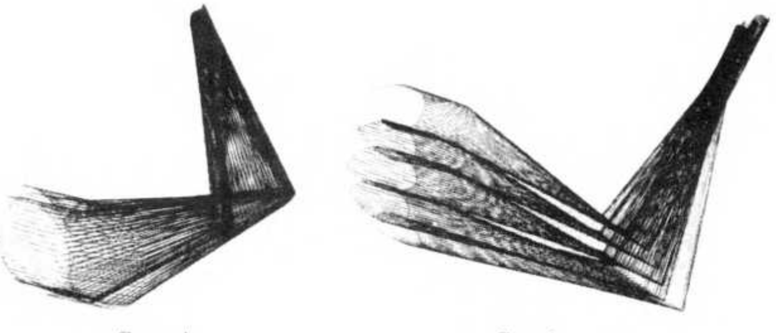

Control Case 1

FIG. 4. Three-dimensional reconstruction of motions of the hand and arm for the gesture WIND. Note added downward movement axis by Case 1.

Apraxic patients also demonstrate variability in their movements. Such behaviour is clearly seen in fig. 5, which presents the reconstructed movement of the gesture WIND by Case 1 versus a control subject. Fig. 5 shows that he produced repeated circular movement paths, but constantly changed their amplitudes and spatial orientations. Fig. 5 also illustrates the large variability across movement replications shown by the apraxic subjects. Figs 4 and 5 present 2 replications of the gesture WIND by Case 1 and by 1 control subject. The variability in movement path and planar orientation shown by Case 1 is marked, and such variability was regularly seen in the movements of the paraxic subjects.

Impairments in joint control. In addition to making spatial orientation errors, the spatial trajectory of an apraxic's limb when making a pantomime is often incorrect (Rothi *et al.*, 1988). This spatial error may be related to the incorrect use of the musculature that moves certain joints and keeps others stabilized. To examine relative use of proximal versus distal musculature by the apraxic subjects to control their movements, we asked whether the apraxic subjects may be attempting to control their distal musculature via their proximal muscles. The gesture 'unlock a door' provides a good starting point for this analysis. The control subjects generate the twisting portion of the movement distally from the elbow. Fig. 6 presents reconstructed movements of the arm in this gesture

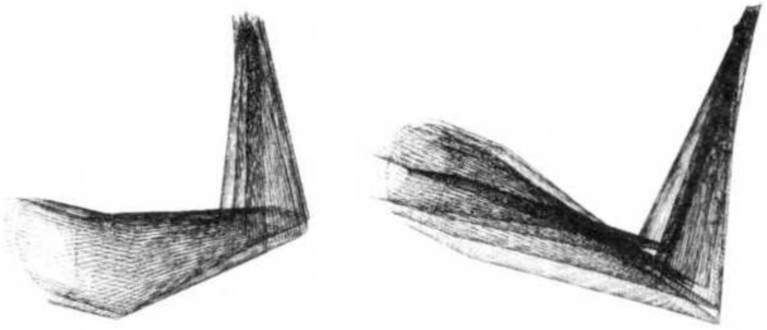


FIG. 5. Three-dimensional reconstruction of the motions of the hand and arm of a control subject and Case 1 performing the gesture WIND. Note searching behaviour of the apraxic subject.

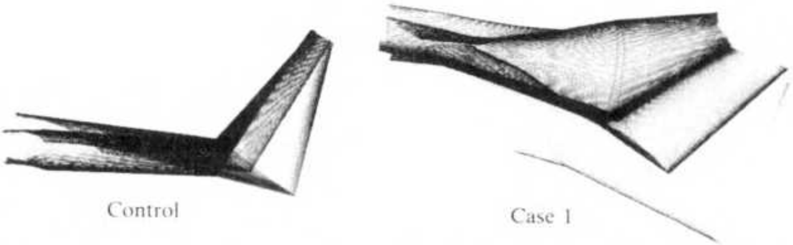


FIG. 6. Three-dimensional reconstruction of motions of the hand and arm of a control subject and Case 1 performing the gesture KEY. Note large displacement of the elbow by the apraxic subject as compared with the control.

for a control subject and for Case 1. The control subject shows a small elbow displacement, in contrast to Case 1 who exhibits a very large elbow displacement.

The twist portion of each movement was edited out graphically so that it could be analysed directly. To determine the degree to which the movement was generated at the shoulder as opposed to the elbow, the maximum displacement of the hand and elbow was measured. If the movement is generated distally, there should be larger hand than elbow movement. If the movement is generated proximally at the shoulder, there should be an opposite pattern. Fig. 7 presents the maximum displacement of the hand and the elbow, across trials, for a control subject and for Case 1.

Fig. 7 shows that the control subject has substantially larger hand than elbow displacements across movement replications. In contrast, Case 1 shows exactly the opposite pattern. To quantify the relative displacements of hand and elbow movement, the ratio of hand-to-elbow displacement for the twist portion of the movement was calculated for each trial, for each control subject and for Case 1. (These ratios could not be obtained from Case 2 because he did not produce a twist portion of the movement; he instead produced small, circular motions of the entire arm, generated proximally at the shoulder.) The mean hand-to-elbow displacement ratio for the control subject was 1.86, indicating almost twice as much hand as elbow movement. The mean ratio for Case 2, however, was 0.73, reflecting greater elbow than hand motion. His mean ratio was significantly different from that of the control subjects [t(20) = 2.2, $P < 0.05$]; indeed there was no overlap in the two ratio distributions. These data indicate that whereas the control subjects were generating the movement distally from a point axis at the elbow, Case 1 was generating it proximally at the shoulder.

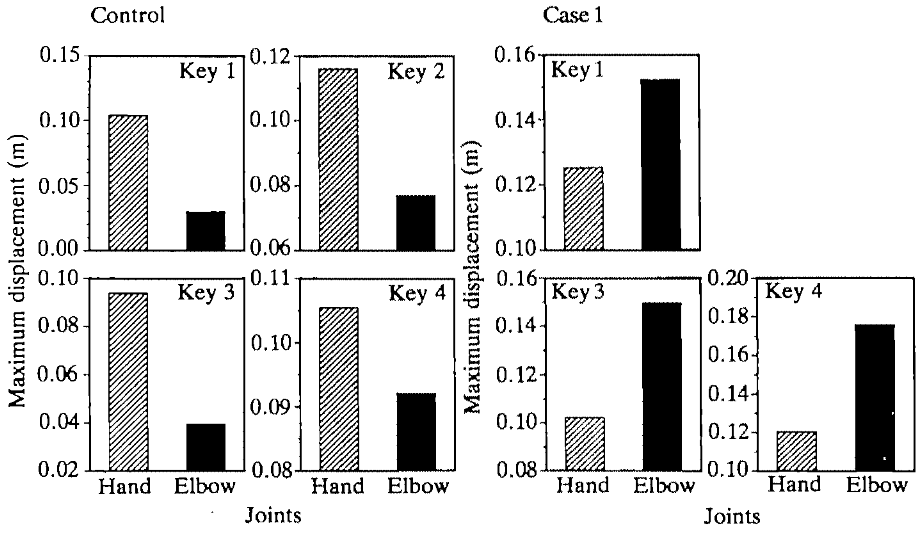


FIG. 7. Maximum displacements of the hand and elbow across trials for the twist portion of the gesture KEY of a control subject and Case 1. The apraxic subject shows larger elbow than hand displacements in contrast to the control.

Spatial errors could occur not only because the wrong joint is moved but also because when multiple joints may be moved there is poor coordination. The apraxic subjects do show poor coordination of shoulder and elbow motions, often with minimal elbow flexion and extension. For example, the gesture CARVE requires coordinating flexion and extension at the shoulder with flexion and extension at the elbow. Fig. 8 presents the variation in elbow flexion and extension during the course of the gesture CARVE. The profile of the control subject is reasonably sinusoidal with a moderately large 30 deg displacement. The profile of Case 2, however, is irregular and has extremely small angular changes.

The average angular change per cycle of movement was calculated across subjects and trials, and is shown in fig. 9. Fig. 9 shows that both apraxic patients had minimal angular change at the elbow relative to the control subjects. The average angular changes for Cases 1 (6.2 deg) and 2 (5.7 deg) were significantly smaller than that of the control subjects (26.7 deg) [$t(64) = 10.0, P < 0.001$; $t(48) = 7.7$, $P < 0.001$, respectively]. Thus here, too, the apraxic subjects seem to be generating the movement proximally

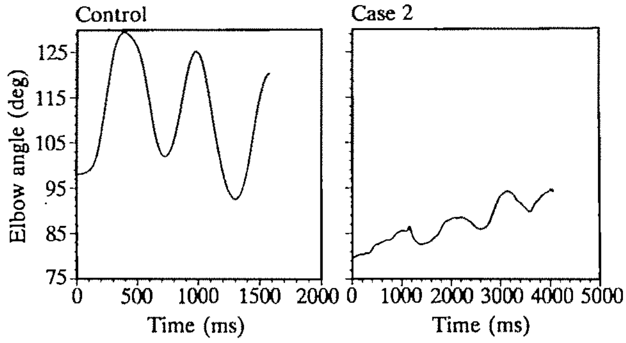


FIG. 8. Elbow flexion and extension during the gesture CARVE of a control subject and Case 2. Note small irregular angular changes of the apraxic subject.

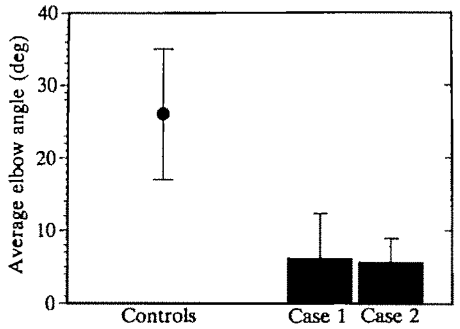


FIG. 9. Average angular change in elbow flexion and extension per movement repetition cycle of the gesture CARVE across subjects and trials. One SD about each mean is shown. Note the substantially reduced angular change at the elbow by the apraxic subjects.

rather than distally, as if they are relying on their proximal musculature to control the distal.

Temporal errors

Difficulties in movement initiation and searching for target motions. The apraxic subjects show impairments not only in the spatial orientation of their movements but also in the initiation and timing of movement. In many cases the apraxic subjects display an initial hesitation before the movement is fully begun, often revealed by a very slow initial build-up of hand velocity. Fig. 10 illustrates one such case. This unusually slow build-up of velocity was seen frequently in the apraxic subjects.

Interestingly, we have observed movement initiation difficulties not only at the beginning of a movement but also within the movement at points of transition between movement components. Fig. 11 presents the reconstructed motion of the arm, together with tangential hand velocities and accelerations, of a control subject and of Case 1 performing the gesture ERASE. Whereas the control subject has very smooth transitional movements between the lateral sweeping motions of the gesture, Case 1 appears to hesitate at the points of turn-around between lateral sweeps, having difficulty initiating the subsequent lateral motion. At the turn-around points, Case 1 produces repeated low amplitude oscillations before initiating the next movement component.

Impairments in movement timing. Normal human movement has fluidity and precision that breaks down in apraxia. The three-dimensional stroboscopic reconstructions of

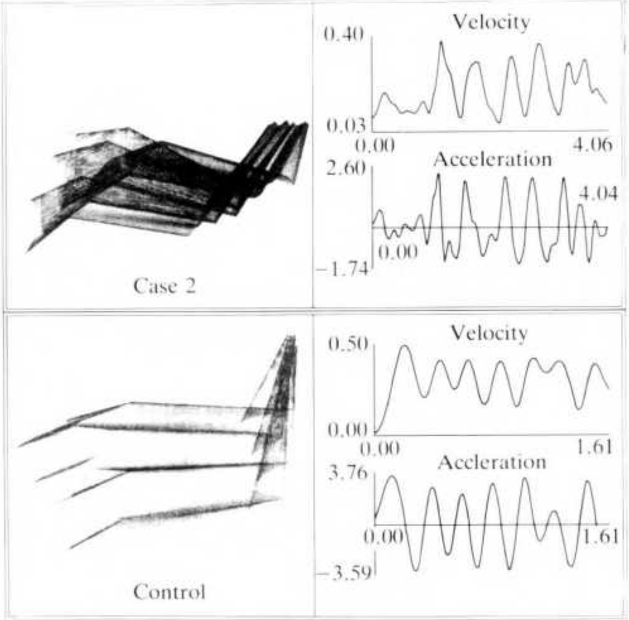


FIG. 10. Three-dimensional reconstruction of motions of the hand and arm of a control subject and Case 2 performing the gesture CARVE. Tangential velocity ($m \cdot s^{-1}$) and acceleration ($m \cdot s^{-2}$) of the hand are also presented. Case 2 shows an initial period of slow velocity, reflecting an initial hesitation before the movement is fully begun.

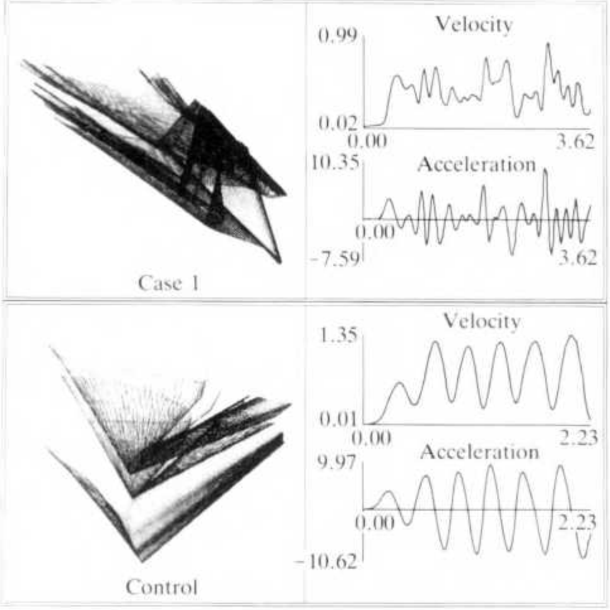


FIG. 11. Three-dimensional reconstruction of motions of the hand and arm of a control subject and Case 1 performing the gesture ERASE. Tangential velocity (m·s^{-1}) and acceleration (m·s^{-2}) of the hand are also presented. Note points of repeated low amplitude oscillations in the trajectory of Case 1 at points of turn-around between lateral sweeps.

movement uniquely capture this fluidity, or lack of fluidity, visually. For example, the reconstructions of the gesture CARVE by Case 2 and a control subject (presented in fig. 10) clearly show the smoothness of the movement of the control subject and the irregular and nonfluid motion of Apraxic E.T.

To quantify this nonfluidity of movement, the tangential hand velocity profiles for the four replications of the gesture CARVE for a control subject and Apraxic E.T. are presented in fig. 12. Fig. 12 shows that the hand velocity profile of the control subject is reasonably sinusoidal, reflecting smooth repetitive movement. The velocity profile of Case 2, in contrast, is nonsinusoidal. It has many irregularities (CARVE 1 and 2), double peaks (CARVE 3), and much local variation (CARVE 1−4), reflecting the awkward, nonsmooth movement.

Temporospatial errors

Decoupling of normal space-time relations. Movement trajectories may be described in terms of their spatial path and the time sequence along that path. A strict relationship exists betwen these two movement attributes: hand velocity is tightly coupled to a spatial aspect of the trajectory, namely its curvature or degree of bending (Viviani and Terzuolo, 1982; Morasso, 1983). This relationship is not due to any physical law but rather has been related to a control process by which complex trajectories are planned through proportional control of velocity and curvature (Viviani and Terzuolo, 1982). We have

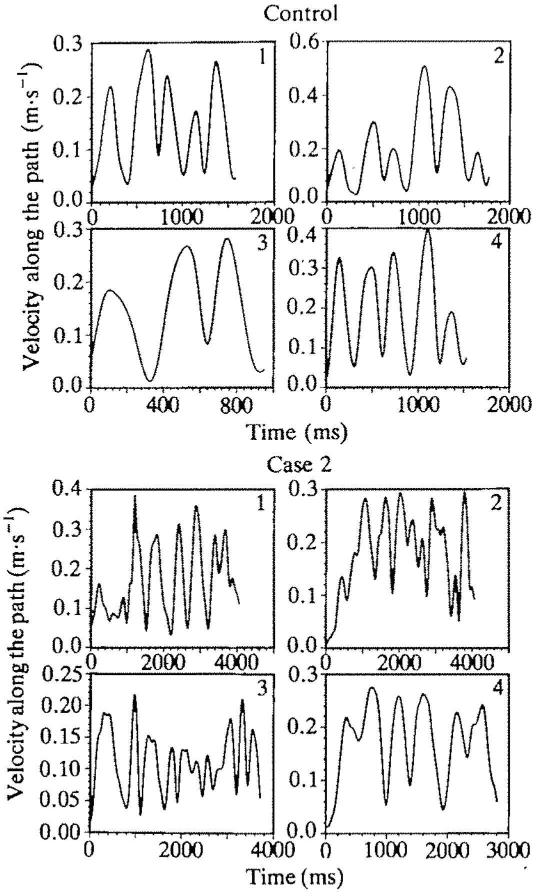


FIG. 12. Tangential hand velocity profiles for the four replications of the gesture CARVE of a control subject and Case 2. The velocity profiles are much less sinusoidal in the apraxic than in the control subject.

found that this space-time coupling breaks down in apraxia. Fig. 13 presents the temporal course of hand velocity and radius of curvature for a control subject and for case 2 performing the gesture CARVE. (Radius of curvature, the inverse of curvature, is plotted rather than curvature so that it may be plotted on the same axis as velocity.)

Fig. 13 shows that for the control subject, there is a strict correlation between velocity and curvature: as velocity increases, curvature decreases. Further, the figure shows that this relationship is decoupled in the apraxic subjects. To capture the linkage between the curves, a computer algorithm was written to locate and mark velocity minima and radius of curvature minima. The filled circles in the figure mark these minima. The times of occurrence of the velocity minima were noted, and the difference in time between each velocity minimum and the nearest radius of curvature minimum was computed. These time differences are plotted in the lower panel. Whereas the time correspondence between minimum velocity and peak curvature was almost perfect for control subjects,

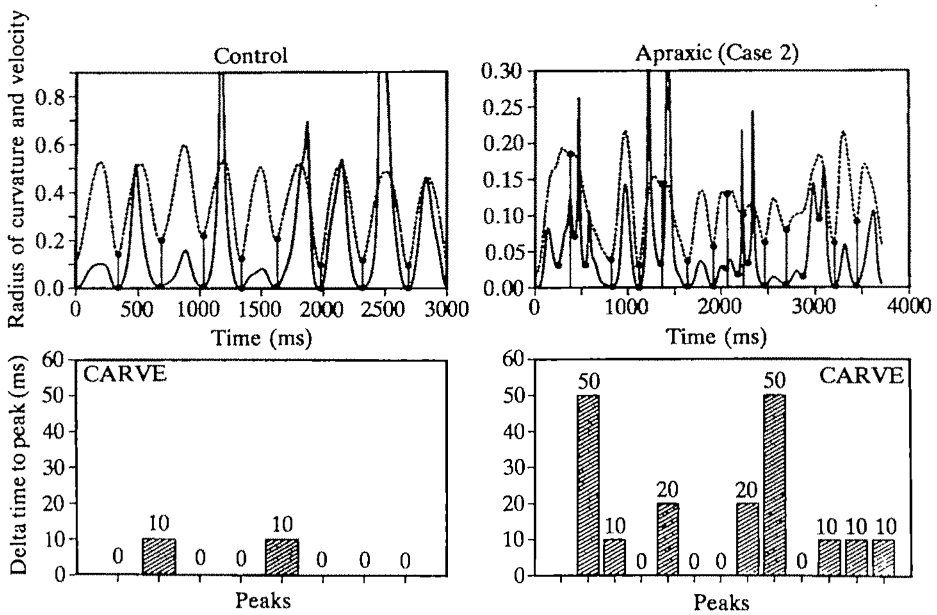


FIG. 13. Velocity-curvature decoupling in the movement of Case 2. Tangential hand velocity ($m \cdot s^{-1}$, broken lines) and radius of curvature (m, continuous line) are plotted in the *upper panels*. Time correspondences between velocity minima and radius of curvature minima are plotted in the *lower panels*.

there was a substantial and consistent lack of such correspondence in the apraxic subjects. Indeed, across gestures and movement replications, the apraxic subjects showed significantly less coupling between velocity and curvature than did the control subjects [for the gesture CARVE, $t(138) = 5.3, P < 0.001$; $t(125) = 4.5, P < 0.001$ for Cases 1 and 2 versus the control subjects, respectively; for the gesture ERASE, $t(159) = 5.7, P < 0.001$; $t(111) = 5.0, P < 0.001$ for Cases 1 and 2 versus the control subjects, respectively]. Inspection of the relationship between hand velocity and radius of curvature reveals that the points at which the apraxic subjects show decoupling between them occur when the velocity profile is least sinusoidal.

DISCUSSION

This investigation presents the first three-dimensional analysis of movement abnormalities associated with apraxia. The three-dimensional computergraphic reconstructions of movement presented here capture some key aspects of the movement errors in apraxia, and represent three-dimensional pictures of the disorder. These motion analysis techniques can extract and isolate certain aspects of movement and thereby allow analysis of movement impairments separate from any error of a configurational nature. It has been postulated that structures within the left cerebral hemisphere contain spatiotemporal representations of purposive skilled movements. Studying the movement of apraxic patients who have damage to these left hemisphere structures brings us closer to an understanding of the nature of these representations.

In general, the errors appear to be of three types: spatial, temporal, and the relationship between the spatial and temporal aspects of movement. A prominent spatial error was the planar orientation of the movement. When someone learns to use a tool or instrument, this is learnt for use in a specific spatial relationship to the body. For example, when using a carving knife, it is usually moved in a sagittal plane. The apraxic subjects, however, often produced movements improperly orientated with respect to the body, lacking proper control over the spatial orientation of movement.

In order to move a tool and instrument correctly, the individual must stabilize certain joints and move others. If the wrong joint or joints are moved, the spatial trajectory will be incorrect. With respect to control of the various joints of the arm, the apraxic subjects tended to use proximal musculature to control the distal. This was seen, for example, on the twist portion of the gesture KEY, where there was substantially greater elbow than hand movement in the apraxic subjects, but an opposite pattern in the control subjects. The apraxic subjects were generating the movement proximally at the shoulder, whereas the control subjects generated the movement distally, from a point axis at the elbow. Many skilled movements require not only that the correct joint be used, but that two or more joints be used in concert. If they are not, then again the spatial trajectory will be incorrect. The apraxic subjects did not coordinate shoulder and elbow motion properly. They showed significantly less angular change at the elbow than did the control subjects, as seen with the gesture CARVE, for example. This gesture requires coordinating flexion and extension at the shoulder and elbow. Because the joints were not well coordinated, the apraxic subjects appeared to make primarily chopping movements. Furthermore, the apraxic subjects generated the movement proximally at the shoulder rather than distally, again as if they were relying on proximal musculature to control the distal. Since the data show distal movement to be more impaired than proximal movement in apraxia, the distal aspects of a movement representation may be more lateralized than the representation of proximal aspects.

Control over temporal variables such as movement initiation, movement fluidity, and movement timing were also disrupted in the apraxic subjects. There was often an initial hesitation before the movement was begun, and then a searching or groping behaviour for the appropriate movement. Such behaviours have been described for apraxia of speech, and the present data demonstrate their applicability for limb apraxia as well. Although searching or groping may be related to their inability to activate the spatial parameter of the movement, the apraxic subjects' hand velocity profiles also showed irregularities that cannot be related to their spatial disturbances. For example, the apraxics' movements were much less sinusoidal than those of the control subjects. Sinusoidal motion for repetitive movement may indeed reflect an organizing principle that the motor system adopts (Nelson, 1983; Hogan, 1984). The system for the generation of such smooth sinusoidal movement appears to break down in apraxia.

A particularly interesting aspect of the nature of space-time representations for learned movement lies in the interrelation of spatial and temporal representations. In normal subjects, a strict relationship exists between these two movement attributes: hand velocity is tightly coupled to the degree of curvature of the trajectory. This correlation seems related to a control process whereby complex trajectories are planned through proportional control of velocity and curvature (Viviani and Terzuolo, 1982). We have shown that this space-time coupling is disrupted in apraxia. Whereas control subjects showed tight linkage between velocity and curvature, the apraxic subjects often showed substantial decoupling between these two movement attributes. Indeed, the points at which the apraxic subjects seemed to show decoupling between velocity and curvature occurred when the velocity profiles were least sinusoidal. These data suggest that in the motor control hierarchy, proportional control over velocity and curvature is dependent on sinusoidal motion.

Due to the data-intensive nature of the analysis, we studied only 2 subjects with apraxia, and both had large lesions. Future studies must determine the degree to which various spatial and temporal attributes of learned movement are represented together or are represented independently of one another. If spatial and temporal representations are contained in one anatomical area, disruption of spatial and temporal attributes should always occur together. If they are represented independently, there should be disruption of one attribute independently of the other. Finally, since we studied the left hand and arm in 2 subjects who were free of right hemisphere lesions, it would appear that in these 2 subjects the right hemisphere, by itself, does not contain all the information to program the spatial or temporal aspects of skilled movements.

ACKNOWLEDGEMENTS

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MOTOR LEARNING IN PATIENTS WITH CEREBELLAR DYSFUNCTION

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SUMMARY

This study examined whether cerebellar dysfunction resulted in deficiencies of motor learning. Patients with cerebellar atrophy only or cerebellar atrophy combined with atrophy of the brainstem and age-matched normal subjects performed two tasks to assess improvements in skilled performance. The first task was repetitive tracing with the hand of an irregular geometric pattern with normal visual guidance, and the second task was repetitive tracing of a different geometric pattern with mirror-reversed vision. Patients with pathology limited to the cerebellum showed impairments in the skilled performance of the movement performed with normal vision that may have been related to a failure to alter movement strategy. Patients with added pathology in the brainstem exhibited impairments in adapting to mirror-reversed vision. Subsidiary experiments indicated that improvements of movements guided by mirror-reversed vision were mediated by vision. These results indicate that the cerebellum and its associated input pathways are involved in motor skill learning.

INTRODUCTION

Evidence has been accumulating that the cerebellum and its input and output pathways play a significant role in motor learning. The anatomical regularity and precision of the inputs to the Purkinje cells, the output neurons of the cerebellar cortex, suggest that the cerebellum could be a substrate for adaptive behaviour and especially motor learning (Brindley, 1964; Eccles *et al.*, 1967). Marr (1969) hypothesized that the two main inputs to the Purkinje cells of the cerebellar cortex, the climbing and mossy fibres, provide distinctive signals in the establishment and maintenance of associative events. Marr (1969), and later Albus (1971), suggested that the climbing fibre inputs to the Purkinje cells, originating in the inferior olive, provide 'teaching' signals and that the mossy fibre inputs, originating in the pontine nuclei, provide important contextual information to form new associations based on the climbing fibre inputs to the Purkinje cells. Gilbert and Thach (1977) provided some indirect evidence for these theories by showing that complex spike activity of Purkinje cells, which reflects the climbing fibre input, is transiently increased in some cells when animals are actively adapting to a new movement situation.

Evaluation of the cerebellar contribution to the plasticity of the vestibulo-ocular reflex and to the formation and retention of the classically conditioned nictitating membrane

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response has contributed significantly to understanding the role of the cerebellum in adaptive behaviour. Although the site of the 'plastic' synapse involved in vestibulo-ocular reflex adaptation has been suggested to be either in the flocculus (Ito, 1982) or the vestibular nuclei (Lisberger and Pavelko, 1986), it is nevertheless clear that cerebellar mechanisms are important in adaptation of visuomotor reflexes (Stone and Lisberger, 1986). Additionally, the work on the conditioned nictitating membrane response has generally supported the Marr-Albus models. In particular, stimulation of climbing fibres can act as an unconditioned teaching stimulus (Mauk *et al.*, 1986), whereas stimulation of mossy fibres can act as a conditioned learning stimulus (Steinmetz *et al.*, 1986; Lavond *et al.*, 1987*a*). In contrast, lesions confined to the cerebellar hemisphere only transiently disrupt the acquisition and retention of the nictitating membrane response (Lavond *et al.*, 1987*b*; but *see* Yeo *et al.*, 1985). Thus, for the nictitating membrane response at least, the cerebellar cortex appears to integrate the major brainstem inputs but does not appear to be necessary for retention of the conditioned nictitating membrane response.

There have been numerous descriptions of the deficits in voluntary and involuntary movement disorders of the limbs and eyes in humans with cerebellar dysfunction (Holmes, 1917, 1939; Hallett *et al.*, 1975; Selhorst *et al.*, 1976; Beppu *et al.*, 1984, 1987; Friedemann *et al.*, 1987; Sanes *et al.*, 1988). In contrast, there has been a paucity of studies concerned with motor learning in these patients. Those studies that have been done have mostly been concerned with motor adaptation to altered visual environment (Gauthier *et al.*, 1979; Weiner *et al.*, 1983). In the latter study, cerebellar patients exhibited poorer than normal short-term adaptation when they wore distorting prisms and also had smaller than normal visuomotor after-effects when the prisms were removed. It is also likely that patients with cerebellar dysfunction have deficits in the learning of new skills, as suggested by Marr (1969). In the present study, we evaluated a series of patients with cerebellar disease on two tasks of skill acquisition, including one in which complex movements were made with reversed vision.

METHODS

Subjects

Eleven patients, aged 18–70 (mean 48.5) yrs, presenting with clinical signs of cerebellar dysmetria in the upper extremities and 8 age-matched normal controls, aged 20–66 (mean 44.3) yrs, participated in these experiments. The patients were divided into two groups according to clinical and diagnostic criteria: group 1 consisted of patients with cerebellar hemisphere and/or vermis atrophy, and group 2 included patients with olivopontocerebellar atrophy syndrome (OPCA). The patients in group 1 were considered to have pathology limited to the cerebellum itself, whereas the patients in group 2 had atrophy both in the cerebellum and medullary and pontine regions of the brainstem. The patients' clinical descriptions are shown in Table 1. None of the patients exhibited tremor as a clinical symptom. Informed consent according to an NIH committee on human experimentation was obtained from all participants. All subjects were naive with respect to the design and goals of the study.

Apparatus

A GTCO digitizing tablet coupled with an electromagnetic stylus was used to measure reaching movements of the arm. The tablet, with its embedded electromagnetic search coil, had an active square-shaped

TABLE 1. CLINICAL DESCRIPTION OF THE CEREBELLAR PATIENTS

Case	*Age (yrs)/sex*	*Diagnosis*	*Radiological findings*	*Upper limb ataxia*
Group 1 (cerebellar hemisphere pathology)				
H1	55 F	Cerebellar degeneration, autosomal recessive pattern	Hemisphere and vermis atrophy[b]	Moderate
H2	67 M	Cerebellar degeneration, sporadic type	Slight hemisphere atrophy[a]	Moderate
H3	18 M	Cerebellar degeneration, sporadic type	Diffuse cerebellar atrophy[b]	Severe
H4	70 M	Cerebellar degeneration, sporadic type	Midline atrophy[a]	Moderate
H5	29 M	Cerebellar degeneration, sporadic type	Hemisphere and vermis atrophy[b]	Moderate
H6	67 F	Cerebellar degeneration, autosomal dominant pattern	Mild diffuse cerebellar atrophy[a]	Mild
H7	51 M	Cerebellar degeneration, alcoholic aetiology	Hemisphere and vermis atrophy[a]	Mild
Group 2 (OPCA)				
O1	45 F	OPCA, autosomal dominant pattern	Cerebellar and brainstem atrophy[a]	Moderate
O2	56 F	OPCA, sporadic type	Cortical atrophy with mild pontine atrophy[b]	Mild
O3	56 F	OPCA, sporadic type	General cerebellar and pontine atrophy[b]	Moderate
O4	20 F	OPCA, sporadic type	Marked hemisphere and vermis atrophy; moderate atrophy of pons, medulla and upper spinal cord[b]	Moderate

[a] Computed tomography. [b] Magnetic resonance imaging.

measurement field of 0.258 m^2. The stylus, which emitted an electromagnetic wave and resembled a fountain pen, was used to evaluate the location of the hand by providing X and Y coordinates via an interface attached to the tablet. A glass plate was placed over the digitizing tablet, and the stylus was fitted with a nylon tip to allow it to slide with relatively low friction across the glass. The spatial accuracy of the system was nominally 0.25 mm, and spatial coordinates were digitized at 100 Hz. The tablet was mounted on a tilt table that was tilted at about 10° towards the subject. A frame mounted on the far end of the tilt table could hold a mirror that was used in the mirror adaptation experiments. For these experiments, the hand was hidden from direct view by having the subject place the right hand in a U-shaped wooden enclosure on the data tablet.

Procedures

Three separate experiments were conducted in two sessions, each lasting from 15 to 60 min. For each experiment, subjects traced with the point of the stylus an irregular geometric pattern that appeared on a piece of paper placed directly onto the tablet (fig. 1). Patients used the right hand throughout the motor skill evaluation. The patterns were sufficiently large so that subjects had to move more than the fingers and wrist to accomplish the task. Typically, the movement involved shoulder and elbow joint rotations, as well as adjustments of the wrist and occasionally the fingers. Speed of execution was emphasized as the most important movement parameter. Subjects were instructed to slide the stylus across the data tablet as rapidly as possible, but with the proviso that each movement segment begin and end in the small squares that enclosed each vertex of the pattern. Subjects were cautioned not to pause at the vertices, but rather to execute the movement in one continuous sequential movement. Subjects were informed that the lines

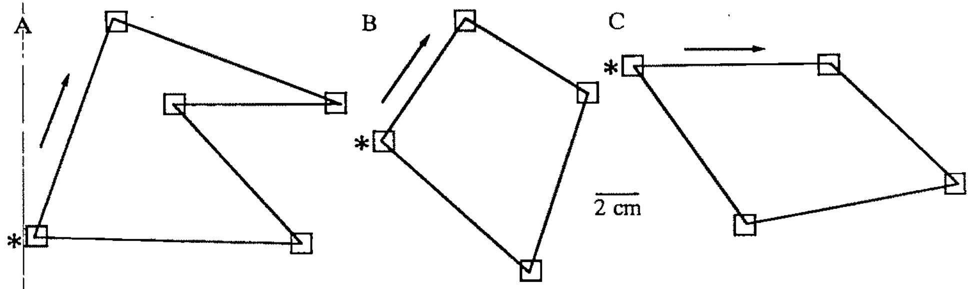

FIG. 1. Patterns used for tracking movements. A, tracking pattern for movements with normal vision. For this and subsequent patterns, the asterisk is next to the starting position, and the arrow (not shown on the patterns viewed by the subjects) designates the requested direction of movement. The squares surrounding the vertices were target zones for the beginning and end of each segmental movement. B, pattern used for the first set of mirror tracking movements. C, pattern used for the second set of mirror tracking movements.

connecting the vertices were intended as a general guide for the sequential movement. In practice, most segments did begin and end in the squares, although this was not always evident for the highest velocity movements and for movements made with mirror vision. The room lights were dim at all times. No practice trials were allowed for any of the patterns. Subjects performed the series of sequential movements with typically no more than 5 s between successive movements, although longer rest periods were allowed at any time. In the first session, subjects traced a 5-vertex pattern (fig. 1A) with normal visual guidance for 50 movements. In the second session, subjects traced a 4-vertex pattern (fig. 1B) without direct visual guidance, but instead viewed the hand and the pattern with a mirror placed in front of them while performing 50 repetitions of moving around the 4-vertex pattern. Then a new 4-vertex pattern was presented (fig. 1C), and they performed 10 additional movements with the mirror-reversed vision. One of the normal subjects was not tested with the 5-vertex pattern. Data from all cerebellar patients were collected successfully on all tasks.

Data analysis

X and Y coordinate data and the tangential velocity of the hand from each sequential movement were inspected on a computer display. Minima in velocity that corresponded to the end of one segment and to the beginning of the next movement segment were marked with an electronic cursor. The total movement time (MT, 10 ms resolution) required to complete the movement, the average, peak, and end-point error per segment, and the number of times the tangential acceleration crossed zero during the complete trajectory were obtained. This last measure was a crude indication of movement smoothness, insofar as repeated start-stop movements during the trajectory and even limb ataxia of significant magnitude would be reflected in an accumulation of zero crossings in the tangential acceleration profile. Average error was the sum of the perpendicular distance for each digitized X-Y sample from an ideal path between two vertices divided by the number of digitized sample points required to complete that segment. The procedure to calculate average error with respect to the number of sampled points was used to avoid inappropriate error scores due to the total time taken to complete the movement. If time was not considered in the calculation, then a trajectory that was, for example, 1 cm away from ideal and completed in 1 s (100 sample points) would have the same error score as a trajectory that was 0.5 cm away from ideal and completed in 2 s (200 sample points). If an observed coordinate was beyond the region in which a perpendicular distance could be obtained, then the straightline distance between the coordinate and the nearest vertex related to the movement segment was derived and summed to the total. No consideration was given to whether individual coordinates were inside or outside the pattern. The segmental errors were summed to derive error scores for the complete movement. Two separate repeated measures analyses of variance were done for each measured variable;

one was for the first 15 trials and the other was for all 50 trials, blocked into groups of 5 trials each. These data were expressed as a percentage of the first trial (15 trial analysis) or the average of the first 5 trials (50 trial analysis). Linear correlation methods were used to compare the results from the first two experiments and for comparisons between MT and accuracy data or acceleration zero crosses. The rationale for using normalized data were twofold. First, there was a wide, and overlapping, range of response times and accuracy scores among the three groups and specifically a few patients showed very long times for the first few trials in the mirror adaptation task. Secondly, this investigation was concerned with the magnitude of behavioural change independent of a subject's performance level. Thus the absolute level of performance, because of overlapping scores, could have easily obscured any significant results in relation to behavioural adaptation. Despite our primary concern with relative scores, we do report the analyses of absolute performance. Unless noted, the data reported are on the normalized data. Reporting of the raw data values is prefixed with the word 'absolute'.

RESULTS

Normal vision

The major features of the repetitive performance with normal vision are shown as sample trajectories in fig. 2 and as averaged data in fig. 3. The normal subjects and both patient groups decreased the MT needed to track the pattern with movement repetition ($P \leq 0.05$). However, the analysis of MT showed that the hemisphere patients differed from the normal subjects in performance across the 50 trials. For these patients, the MT scores decreased less than those of the normal subjects ($P \leq 0.0002$). The results of the MT analysis for the first 15 trials were similar to those for the 50 trials (fig. 3B). Although the normal subjects and both cerebellar groups showed improvements in MT over the 15 trials ($P \leq 0.0001$), the hemisphere patients exhibited a slower rate

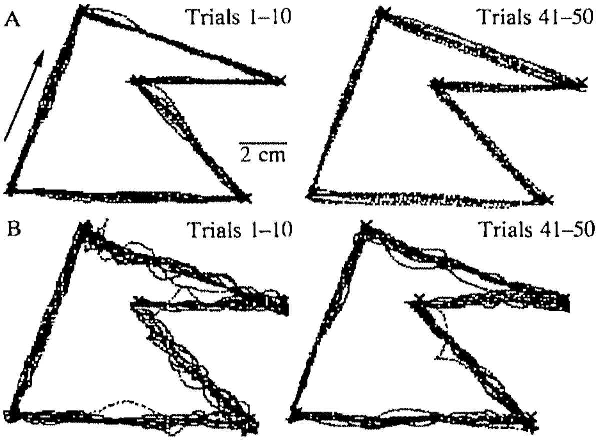

FIG. 2. Movement trajectories with normal visual guidance. A, 10 superimposed movement trajectories from normal subject C51 from the first (*left*) and last (*right*) 10 movements performed with normal vision. The average time required to complete the track was 7.45 s for the first 10 movements and 4.71 s for the last 10 movements. B, 10 superimposed movement trajectories from Case H5 with a pure hemisphere lesion from the first (*left*) and last (*right*) 10 movements performed with normal vision. The average time required to complete the track was 9.58 s for the first 10 movements and 9.85 s for the last 10 movements. Accuracy was unchanged between the first and last 10 movements.

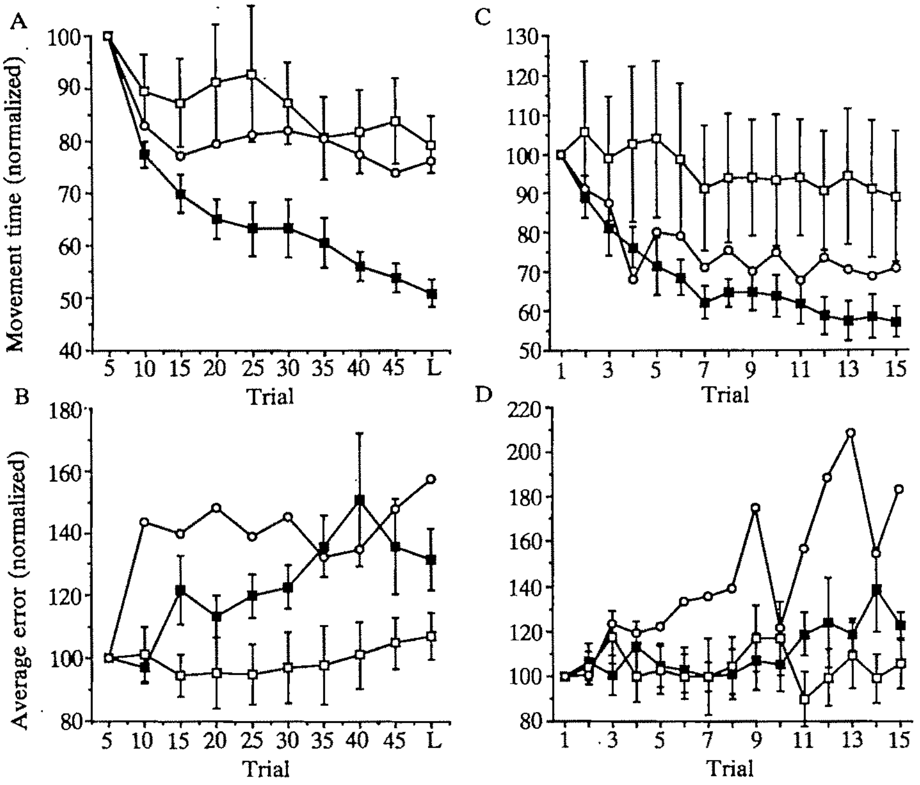

FIG. 3. Movement time (MT) and accuracy during normal vision task. A, average MT to complete moving around the 5-vertex pattern. Each data point represents the average MT (mean ± SEM) of 5 successive trials expressed as a percentage of the average MT on the first 5 trials. This normalization convention is used throughout. Note that the normal subjects exhibited continued improvement in MT across the 50 trials. The error bars were omitted from the OPCA group because of their large size. B, average error during the complete track. The normal and OPCA groups showed increased error, whereas the hemisphere patients exhibited a constant amount of error throughout. C, average MT to complete the movement for each of the first 15 trials. Each data point represents the MT expressed as a percentage of MT on the first trial. Note that all groups reach the approximate asymptotic level of performance within the first 10 trials, although the normal subjects continue to show improvement in MT with trial repetition. D, average error for the first 15 trials. Note that the overall trend observed for all 50 movements is apparent by performance of Trial 15. Closed squares = normals; open squares = hemisphere patients; open circles = OPCA.

of decline in MT than did the normal subjects during the first 15 trials ($P \leq 0.05$).

The absolute MT values in seconds are shown in Table 2. Although the average absolute MT for the OPCA patients was twice that for the hemisphere patients, these groups did not differ from each other in the 50 trial performance. This absence of a statistically significant difference in MT between the two cerebellar groups, and a similar absence of a difference between the normal subjects and OPCA patients, might suggest that the OPCA patients are either intermediate in performance between the normal subjects and hemisphere patients or that the small number of OPCA patients might have impaired distinguishing this group from the normal subjects or hemisphere patients. In this regard, 1 of the 4 OPCA patients exhibited increased, instead of decreased (as did the remaining

TABLE 2. MEAN ABSOLUTE KINEMATIC SCORES FOR THE CEREBELLAR PATIENTS AND NORMAL SUBJECTS ON THE NORMAL VISION AND MIRROR REVERSAL TASK

	Normal vision		*Mirror reversal*	
	Trials 1–5	*Trials 46–50*	*Trials 1–5*	*Trials 46–50*
Movement time				
OPCA	13.32 ± 3.74*	9.09 ± 3.28*	14.26 ± 3.17*	11.14 ± 1.88*
Hemisphere	6.66 ± 0.80*	5.24 ± 0.77	58.37 ± 15.01*	19.05 ± 5.03*
Normal	8.46 ± 0.76	4.35 ± 0.45	19.65 ± 3.31	7.01 ± 1.11
Average error				
OPCA	1.31 ± 0.38	1.72 ± 0.23	2.55 ± 0.24	2.48 ± 0.25
Hemisphere	1.80 ± 0.32*	1.90 ± 0.30*	4.36 ± 0.68*	4.43 ± 1.41*
Normal	1.02 ± 0.26	1.26 ± 0.25	2.36 ± 0.11	2.09 ± 0.26
End-point error				
OPCA	1.55 ± 0.56	2.29 ± 0.44	2.80 ± 0.59*	1.97 ± 0.34
Hemisphere	2.57 ± 0.58*	2.86 ± 0.55*	3.65 ± 0.77*	4.27 ± 1.46*
Normal	1.04 ± 0.39	1.82 ± 0.4	1.83 ± 0.16	2.20 ± 0.48
Peak error				
OPCA	9.32 ± 5.87*	3.34 ± 0.63	12.93 ± 6.30	7.46 ± 2.78*
Hemisphere	4.49 ± 1.13*	4.66 ± 1.08*	24.62 ± 7.46*	20.70 ± 8.79*
Normal	3.04 ± 0.91	2.66 ± 0.55	11.06 ± 3.48	4.13 ± 0.43
Tangential acceleration transitions				
OPCA	37.90 ± 10.67*	19.84 ± 5.74*	40.30 ± 7.59*	33.18 ± 4.48*
Hemisphere	20.54 ± 3.53	15.29 ± 2.71*	247.83 ± 69.81*	74.66 ± 24.25*
Normal	20.00 ± 3.53	11.36 ± 0.66	63.88 ± 11.29	19.16 ± 2.52

* $P \leq 0.05$ in comparison with normal subjects. MT values are expressed in seconds ± SEM, error values are expressed in cm and acceleration transitions are expressed in occurrences.

3 OPCA patients), MT; this may have been the reason that the MT of the OPCA patients was not different from that of the hemisphere patients or normal subjects.

The average error of the normal subjects (figs 3c, d) increased with trial repetition. Clear increases in average error were not apparent for any patient in the cerebellar hemisphere group, but 2 patients with OPCA did exhibit deteriorations in accuracy. These same 2 patients showed the greatest improvement in MT for the OPCA group. The average error scores across trials with repetition of the 5-vertex pattern differed between the hemisphere patients and the normal subjects ($P \leq 0.01$). The results for average error on the first 15 trials were similar to those for the complete 50 trials except that there was no difference between the normal subjects and the patients with cerebellar hemisphere damage. The analyses of peak and end-point error did not reveal any differences in performance with repetition between the normal subjects and either of the two cerebellar patient groups. However, all groups showed a significant increase in end-point error when all 50 trials were considered ($P \leq 0.001$). Only the normal subjects showed an increase in end-point error with repetition for the first 15 trials ($P \leq 0.0001$). The peak error did not change during performance of all 50 trials or for the first 15 trials. The absolute values of the average, end-point and peak error are shown in Table 2.

The change in the number of zero crossings of the tangential acceleration profile with movement repetition paralleled the results for MT. Although all subjects showed a decrease in the number of acceleration zero crosses, that is, increased smoothness of movement with repetition of the 5-vertex pattern, there were significant differences between all groups of subjects. The minimum number of acceleration zero crosses required to traverse the 5-vertex trajectory was 10; by the end of the repetitive movements, the normal subjects achieved nearly optimal performance. The reduction in the zero crosses of the hemisphere patients was significantly less than that of the normal subjects (Patient by Repetition interaction, $P \leq 0.001$). The OPCA patients did not differ from the normal subjects.

The correlation analyses relating MT to average or end-point error in the normal vision task are illustrated in fig. 4. When considering all 50 trials, MT was negatively correlated with both the average (fig. 4A, left) and end-point error (fig. 4A, middle) in the normal subjects ($P \leq 0.01$) and OPCA patients ($P \leq 0.01$), but not for the patients with hemisphere atrophy. Similar results were observed for average error during performance on the first 15 trials (fig. 4B). Only the normal subjects had a significant correlation between average and end-point error during performance on all trials. Although the averaged grouped data indicated significant correlations between several kinematic variables, correlation analyses of individual subjects scores were not entirely consistent with the grouped data. For the relationship between MT and average error, only 2 of the 7 normal subjects showed a significant negative correlation, although 2 of the remaining subjects showed negative correlations that were of borderline significance ($P \leq 0.1$). Three of the 4 OPCA subjects showed a significant negative correlation between MT and average error ($P \leq 0.01$), whereas 2 of the 7 hemisphere patients showed a significant negative correlation between MT and average error ($P \leq 0.05$). During performance of the first 15 trials, only the OPCA subjects had a significant correlation between average and end-point error. MT and the number of zero crossings

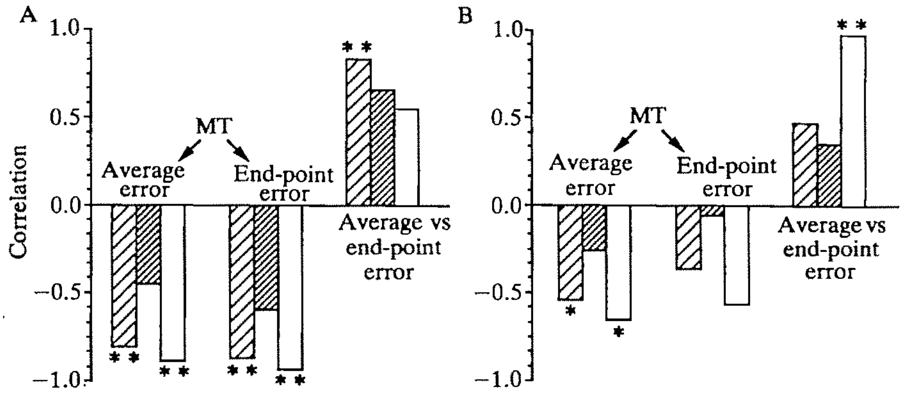

FIG. 4. Correlation analysis of performance variables during the normal vision task. Intercorrelations for MT and average and end-point error. A, comparisons for all 50 trials. B, comparisons for the first 15 trials. Ordinate axis label in B is the same as in A. $^{*}P \leq 0.05$; $^{**}P \leq 0.01$. Broad hatched areas = normals; narrow hatched areas = hemisphere patients; open areas = OPCA.

in the tangential acceleration profile (not illustrated) were highly correlated for all groups of subjects ($r \geq 0.79$, $P \leq 0.001$, combined statistics for the three groups).

Mirror vision

The major features of performance with mirror-reversed vision are shown as sample trajectories from each of the three groups in fig. 5 and as averaged data in fig. 6. The first movements of all groups were slower than performance during the normal vision task. In addition, directional errors were common, especially during the first few trials. The segmental trajectories between the vertices, when performed without major errors in direction, were rarely straight, even for the normal subjects at the end of the 50 trials. Despite this deterioration in performance, in comparison to that observed during normal vision, the normal subjects and both patient groups decreased the total MT needed to track the pattern with movement repetition with mirror-reversed vision ($P \leq 0.05$). The OPCA patients did not improve their MT as much as the normal subjects or hemisphere patients (group by trial interaction, 50 trials, $P \leq 0.05$; 15 trials, $P \leq 0.05$, normal subjects only). However, and in contrast to the results on the normal vision task, the normalized MT performance of the hemisphere patients was nearly identical to that of the normal controls.

The absolute MT values for the mirror reversal movements are shown in the right portions of Table 2. Initially, the OPCA patients had the fastest times, though by the last trials the normal subjects had improved their absolute MT to less than that for the

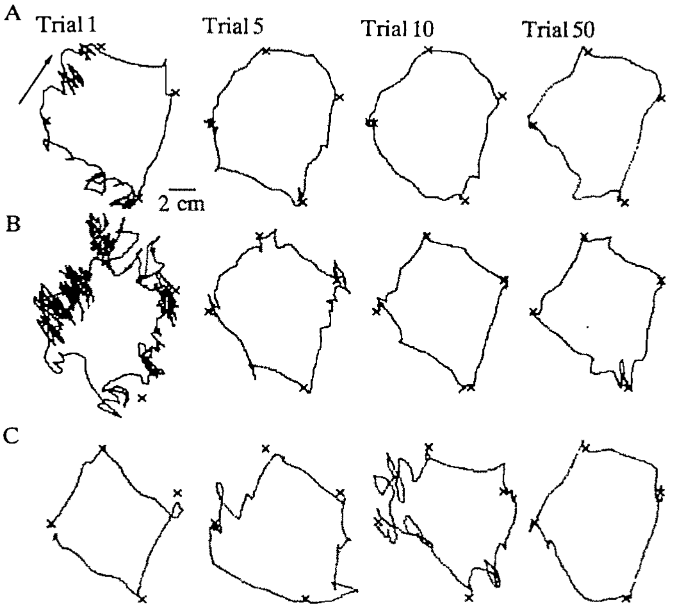

FIG. 5. Trajectories during mirror-reversed vision. A, movements of normal subject C51 are illustrated. B, movements of Case H6 with hemisphere pathology are shown. C, movements of Case O4 with OPCA are depicted. The arrow in part A indicates the required initial direction of movement and each X symbol indicates the vertices of the pattern.

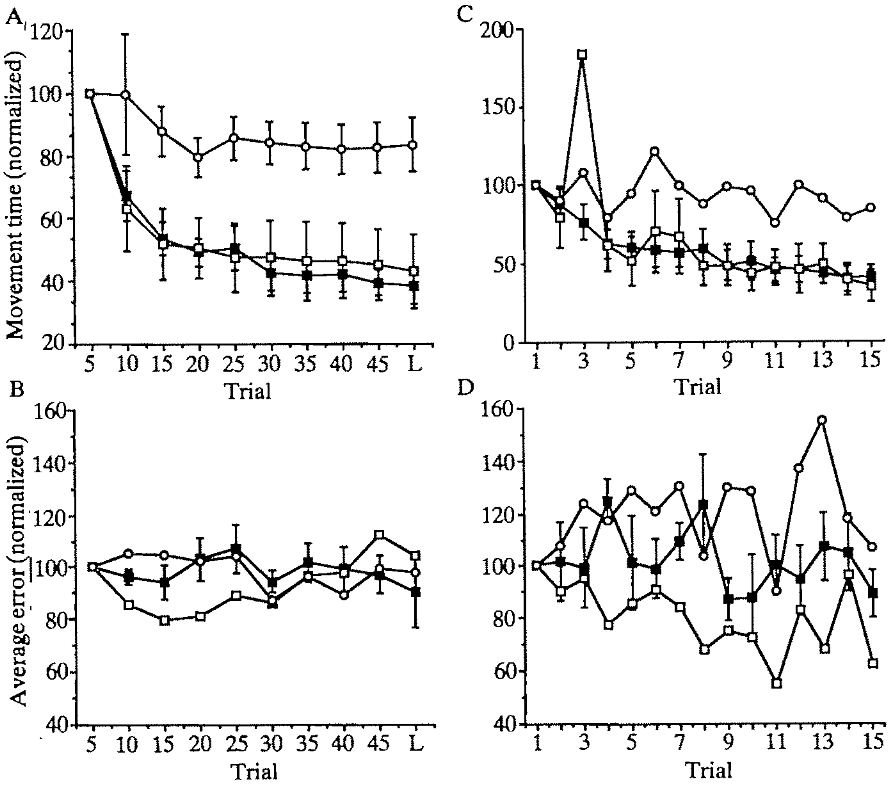

FIG. 6. Movement time and accuracy during mirror-reversed vision task. A, average MT to complete moving around the 5-vertex pattern. The normal and hemisphere groups showed decreased MT with repetition. B, average error during the complete track. No group showed increased error. C, average MT to complete the movement for each of the first 15 trials. Note that all groups reach the approximate asymptotic level of performance within the first 10 trials. D, average error for the first 15 trials. Note that the overall trend observed for all 50 movements was not apparent by performance of Trial 15 and that the variability amongst trials was high for each group. Error bars were omitted from some plots because of their large size. Symbols as in fig. 3.

OPCA group. The hemisphere patients were always slower than the OPCA patients, although their magnitude of improvement was greater than for the OPCA patients.

There were no significant differences in the amount of average, peak, or end-point error between the normal and both cerebellar groups for performance during the 50 trials with mirror-reversed vision. In addition, there were no changes in average error with repetition of performance with mirror-reversed vision for any group. During performance on the first 15 trials, the average error of cerebellar hemisphere patients differed from the normal subjects ($P \leq 0.05$), insofar as the performance of the normal subjects was unchanged from the first to the fifteenth trial, whereas the average error of the hemisphere patients declined by about 40% from the first to the fifteenth trial.

The number of zero crossings of the tangential acceleration profile during the mirror adaptation task paralleled the results for MT. Although all subjects showed a decrease in the number of acceleration zero crosses with repetition of the movement with mirror-guided vision ($P \leq 0.05$), there were significant differences between the groups of subjects. The reduction in the zero crosses of the OPCA patients was significantly less than that of the normal subjects (Patient × Repetition interaction, $P \leq 0.01$). Despite the large absolute number of acceleration zero crosses in the hemisphere patients, there was no difference between the patients and the normal subjects when reduction in the zero crosses was analysed.

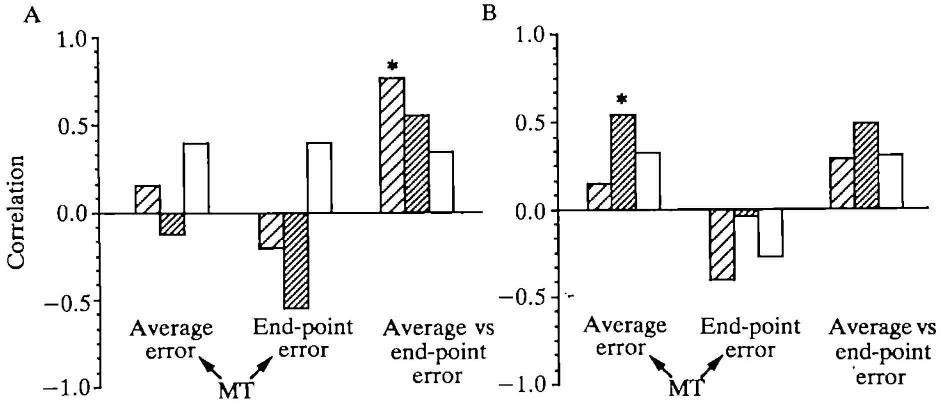

FIG. 7. Correlation analysis of performance variables during the mirror reversal task. A, comparisons for all 50 trials. B, comparisons for the first 15 trials. Ordinate axis label in B is the same as in A. $^{*}P \leq 0.05$. Symbols as in fig. 4.

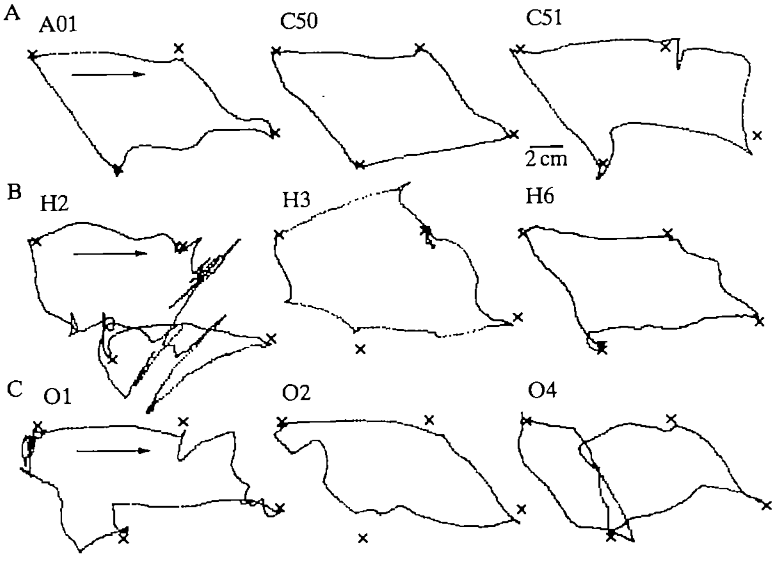

FIG. 8. Movement trajectories using the alternate pattern with mirror-reversed vision (*see* fig. 1C). Representative trajectories of 3 normal (A), 3 hemisphere (B) and 3 OPCA (C) patients for the first in the series of 10 movements. Most subjects (except H3) made little or no error in the direction of the first movement segment as measured 3 cm from the starting point.

The correlation analyses relating MT and average or end-point error in the mirror adaptation task are illustrated in fig. 7. The only significant correlation between MT and an error measure was for the hemisphere patients during performance of the first 15 trials (fig. 7B). Only the normal subjects had a significant correlation between average and end-point error during performance on all trials (fig. 7A). There were no significant correlations between average and end-point error during performance on the first 15 trials. MT and the number of zero crossings in the tangential acceleration profile (not illustrated) were highly correlated for all groups of subjects during performance with mirror-reversed vision ($r \geq 0.81$, $P \leq 0.001$, combined statistics for the three groups).

First trial performance with a second pattern using mirror-reversed vision is shown in fig. 8. This pattern was rotated about 45° with respect to the original mirror-reversed pattern (fig. 1C). Both the normal subjects and the patients, except possibly Case H3, moved in the correct direction and generally with the correct metric on the first trial when presented with this alternate pattern. The average angular deviation from an ideal trajectory of the first movement segment measured 3 cm from the starting point was $0.14 \pm 0.77°$ for the normal subjects, $-1.33 \pm 3.53°$ for the OPCA patients, and $6.67 \pm 3.82°$ for the hemisphere patients. The patients' angular deviation from the expected trajectory did not differ from that of the normal subjects. Over the 10 trials done under mirror-reversed vision with the alternate pattern, there were no differences in the change of MT among the different subject groups.

DISCUSSION

Many studies concerned with the role of the cerebellum in motor learning have focused on the acquisition and retention of simple reflexes or responses (Leaton and Supple, 1986; Thompson, 1986), adaptation of the vestibulo-ocular reflex (Ito, 1982; Lisberger *et al.*, 1984), and in a few cases more complex behaviour involving visuomotor adaptation by humans (Gauthier *et al.*, 1979; Weiner *et al.*, 1983) or learning of a novel skill by monkeys (Gilbert and Thach, 1977). In general, these studies support the notion that cerebellar processes, either intrinsic or involving input or output structures of the cerebellum, are involved in adaptive, and long-term, processes of motor control. Others, however, have argued against a fundamental role for the cerebellum in the establishment of long-lasting associations for motor behaviour (Bloedel, 1987; Lou and Bloedel, 1988). The present results indicate that the cerebellum and related brain structures are involved in motor learning processes.

Motor learning can be classified as motor skill acquisition and motor adaptation. The acquisition of a motor skill can broadly be defined as an improvement in the quality of motor performance, involving accuracy, speed, and a minimum of energy expenditure (Adams, 1987). Furthermore, skill, which is acquired, must be distinguished from the ability to perform, since individual skills often peak at different proficiency levels, although they presumably improve with repetition. These definitions of skill are closely related to voluntary motor behaviour and include the concept of acquiring a new motor ability. Motor adaptation, which includes changes in the vestibulo-ocular reflex and perhaps the speed-accuracy trade-off (Fitts, 1954), involves exchange of one behaviour for another in response to an alteration in either sensory inputs or task demands.

We studied alteration of performance, especially the speed of movement, with repetition of relatively novel movements with normal and mirror-reversed vision, thus permitting assessment of motor learning. Acquisition of a motor skill has occurred when increases in speed are not simply related to a trade-off with accuracy (Fitts, 1954). Increases in speed of movement at the cost of accuracy might be considered motor adaptation.

The aggregate performance strategy of the hemisphere patients differed from that of the normal and OPCA subjects on the normal vision task possibly because the dynamic range of their motor performance, especially regarding MT, is reduced under normal visual guidance conditions. This is supported by the observation that the hemisphere patients were initially operating at a higher speed than normal, and with a higher inaccuracy rate. Although both of these kinematic variables changed moderately with repetition, the diminution of the inverse changes in MT and accuracy, in comparison with normal and OPCA subjects, may have been associated with the hemisphere patients' inability to decrease their MT any further. The restriction of MT is supported by the absence of evidence that they could move faster than the time they showed at the end of the normal vision task. This could be related to the early suggestion that patients with pure cerebellar atrophy are bradykinetic (Holmes, 1917).

Normally there is a trade-off between speed and accuracy in performance of movements with varying amplitude and accuracy requirements (Fitts, 1954). Thus faster movements are often performed with low accuracy, and movements with high accuracy requirements are often performed slowly. These relationships hold for patients with parkinsonism (Sanes, 1985). In the normal vision task, the normal subjects and 3 of the 4 OPCA patients showed the expected inverse relationships between MT and average or end-point error. These two groups of subjects did not exhibit motor skill learning in this task, but instead simply altered their performance strategy. This might be viewed as motor adaptation. In contrast, the patients with cerebellar hemisphere atrophy showed only modest, but qualitatively similar, changes in MT and accuracy by the fiftieth trial.

Jerkiness of the movement trajectories may have contributed to the failure of cerebellar hemisphere patients and OPCA patients to improve their performance on the normal vision and mirror reversal tasks, respectively. One strategy for movement production is to minimize the rate of change of acceleration, or jerk (Nelson, 1983; Hogan, 1984). Indeed, trajectories performed under a minimum jerk strategy have an optimal smoothness (Flash and Hogan, 1985; but *see* Stein *et al.*, 1988). Furthermore, in normal subjects, MT and jerk apparently decrease in parallel with repeated performance of the same movement (Schneider and Zernicke, 1989). Although we did not explicitly measure jerk, the number of zero crossings in the tangential acceleration profiles provides a crude measure of movement smoothness, or movement optimality. That is, a lower number of zero crossings would likely imply a more faithful reproduction of the target trajectory performed with uninterrupted segmental movements. The acceleration zero crossing data indicated that the hemisphere patients had less improvement in movement smoothness than normal subjects on the normal vision task and that the OPCA patients similarly had less improvement on the mirror adaptation task. These results paralleled those for MT, and may have been the causal factor in prolonging MT for the two cerebellar groups on the normal vision and mirror reversal tasks.

The normal subjects showed improved speed but no changes in accuracy on the reversed vision task, a violation of the common performance law of reciprocal changes in speed and accuracy and evidence for true improvements in motor skill. The failure of the OPCA patients to match the MT performance of the normal subjects, and the absence of a change in accuracy for these patients during the mirror-reversed vision task can be interpreted not as a speed-accuracy trade-off but as a deficit in motor skill learning.

Findings from studies concerned with modification of simple behavioural responses in animals with cerebellar pathology offer support for the involvement of the cerebellum and its input structures in the motor skill learning evaluated in the present study. The impairments in forming conditional associations found in animals with lesions to the input pathways of the cerebellum (McCormick *et al.*, 1985; Lewis *et al.*, 1987) could be related to the failure of OPCA patients to learn new associations between the apparent visual world, as distorted by the mirror, and conflicting information from planned movement trajectories and the ensuing kinaesthetic feedback. The associative properties of signals transmitted along either climbing or mossy fibre pathways are supported by observations that electrical stimulation of these pathways substitutes successfully for exteroceptive sensory stimuli that act as conditional or unconditional stimuli (Mauk *et al.*, 1986; Steinmetz *et al.*, 1986; Lavond *et al.*, 1987*a*). Thus it is possible that the transformations necessary to resolve conflict between visual and kinaesthetic inputs gain access to the cerebellum via either climbing or mossy fibre pathways.

Impaired resolution of sensory conflict in cerebellar patients might be related to general difficulties in integration of sensory information in cerebellar dysfunction. It is known that afferent information is transmitted to the cerebellum via climbing and mossy fibres (Gilman *et al.*, 1981; Gellman *et al.*, 1983, 1985; Glickstein *et al.*, 1985; Kim *et al.*, 1986). These inputs, and in particular somatosensory afferent information, may signal changes in environmental conditions (Gellman *et al.*, 1983, 1985). The alterations of Purkinje cell activity due to inferior olivary input observed when monkeys were required to change the muscle activity needed to maintain a relatively static posture (Gilbert and Thach, 1977) could be related to novelty detection. Another possible role of the cerebellum is to integrate sensory inputs with motor commands (Chapman *et al.*, 1986). In this regard, the ability to use visual guidance during ramp or step tracking movements is impaired in patients with cerebellar pathology (Beppu *et al.*, 1984, 1987).

The relative smoothness of the trajectories performed by the OPCA patients on the mirror reversal task was rather surprising. The smoothness was evident on their first trial, even though the performance of the normal and hemisphere patients was grossly impaired (*see* Trial 1 in fig. 5). The significance of these observations is uncertain, but may be related to deficits in visual information processing in the OPCA patients. Visual inputs that normally access the cerebellum via climbing and mossy fibres (Gilman *et al.*, 1981) are probably compromised in OPCA patients. Thus, these patients, unlike normal subjects and cerebellar hemisphere patients, may not have to resolve the discrepancy between proprioceptive inputs and mirror-reversed visual information. Indeed, if OPCA patients rely mostly, but not exclusively, on proprioception for regulation of ongoing movements, then their initial trajectories would be smooth (Beppu, 1987; Sanes *et al.*, 1988). However, the OPCA patients must have used visual information at least to process the directional requirements of the task. Thus it is possible that they used vision in a discrete sampling mode, but relied on proprioception for on-line movement regulation. Additionally, since improvements in skill on the mirror reversal task must entail resolution between the conflicting visual and proprioceptive inputs, patients without the initial conflict would not be expected to exhibit improvements in motor skill. Since the trajectories of the OPCA patients were not as smooth during the mirror reversal task as during the normal vision task, they also relied, but probably less than the normal and hemisphere subjects, on visual information to perform the movements with mirror-reversed vision.

An inability to decrease MT below a minimum imposed by combined cerebellar and brainstem pathology may have kept the OPCA patients from additionally decreasing their MT during repetitive trials in the mirror reversal task. A floor effect that restricted MT would not necessarily explain their performance on the mirror reversal task, since the OPCA patients were able to move faster when they used normal vision than the time recorded at the end of the mirror reversal task (*see* Table 2). Despite this capability, and the observation that the decrease in absolute MT at the end of the mirror reversal task was comparable with that of the normal subjects, the proportionate decrease in MT at the end of the mirror reversal task was much greater for normal subjects than for OPCA patients.

The MT results obtained with the second of two patterns used with mirror-reversed vision indicated that both groups of cerebellar patients, not only the hemisphere group, acquired some information about movements performed under altered visual conditions. Both groups of patients showed equal performance generalization to the new pattern after experience in moving around the first pattern. Further, the patients and normal subjects showed comparable performance on the first segment of the first movement. If, on the second pattern, they had made the first movement in the direction required by the first segment of the first pattern, we could have concluded that MT improvements with movement repetition in the mirror reversal task are dependent, in part, on knowledge of results derived from processing of kinaesthetic information or that all subjects used some visual information to make the movements.

These results support the general conclusion that the cerebellum is involved in learning in the motor system. The patients with pathology limited to the cerebellum showed a deficit in the normal vision task that can be interpreted as their adopting a different strategy than normal controls and might be viewed as a failure of motor adaptation. The patients with combined cerebellar and brainstem atrophy, which probably altered transmission of information to the cerebellum via the climbing and mossy fibres, showed a deficit in the mirror-reversed vision task that can probably be interpreted as a failure in motor skill learning. It appears, as was postulated 25 years ago (Brindley, 1964), that the cerebellum contributes to learning of movement skills, but that the structures providing inputs to the cerebellum are critical in this process.

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Brain (1990), **113**, 121–137

REEVALUATION OF THE ULTRASTRUCTURAL PATHOLOGY OF EXPERIMENTAL CREUTZFELDT-JAKOB DISEASE

SERIAL STUDIES OF THE FUJISAKI STRAIN OF CREUTZFELDT-JAKOB DISEASE VIRUS IN MICE

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SUMMARY

We describe the serial ultrastructural pathology of experimental Creutzfeldt-Jakob disease (CJD) in mice. Spongiform vacuoles, widespread myelin and axonal pathology, accompanied by abundant macrophagic reaction and neuroaxonal dystrophy, were consistently found in mice infected with CJD virus. By contrast, intranuclear vacuolation and swelling of astrocytic and neuronal processes were nonspecific changes that also occurred in control animals. We conclude that CJD-related neuropathological phenomena do not accumulate gradually through the incubation period but develop relatively abruptly and in complete form.

INTRODUCTION

The Fujisaki strain of Creutzfeldt-Jakob disease (CJD) virus passaged in mice is a useful experimental model for the study of this disease, primarily because of its short incubation period. All but one previous ultrastructural study of experimental CJD (Kim and Manuelidis, 1986) have dealt with animals at the terminal stage of disease. Our current perspective of the pathology of CJD, therefore, reflects the devastating consequences of the fully expressed neurodegenerative process. We undertook the present study to examine the serial development of the ultrastructural pathology of experimental CJD in mice. Our data indicate that intranuclear vacuolation and swelling of astrocytic and neuronal processes, previously described as pathological features of CJD (Manuelidis and Manuelidis, 1979*a*, *b*; Kim and Manuelidis, 1983*a*, *b*, 1986), are nonspecific findings, as evidenced by their occurrence in control mice. By contrast, spongiform vacuoles, widespread pathology of myelinated axons accompanied by a robust macrophagic reaction, and neuroaxonal dystrophy are consistently found only in CJD virus-infected mice, and these changes increase in severity.

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MATERIAL AND METHODS

Virus strain, animals and inoculation procedures

The Fujisaki strain of CJD virus, originally isolated from brain tissue of a 56-yr-old man with progressive dementia (Tateishi *et al.*, 1978, 1979, 1980), was passaged three times in mice in this laboratory (Kingsbury *et al.*, 1982). This virus strain is characterized by a short incubation period of approximately 16–18 wks following intracerebral inoculation and by severe destruction of white as well as grey matter in the brain (Liberski *et al.*, 1989*b*). Weanling, 4- to 5-wk-old NIH Swiss mice (Animal Production Area, Frederick Cancer Research Facility, Frederick, MD) were injected intracerebrally in the right parietal area with 0.03 ml of a 10% brain suspension of the Fujisaki strain of CJD virus (titre, 5×10^4 LD_{50} per 0.03 ml). Control animals were injected with 0.03 ml of saline.

Electron microscopy

Two or 3 virus and saline-inoculated animals were sacrificed at weekly intervals, beginning at 1 wk postinoculation, by intracardiac perfusion with 180 ml of 1% paraformaldehyde and 1.5% glutaraldehyde prepared in phosphate buffer (pH 7.4). Animals were then placed at 4° C for 2 h, and brains were removed and rinsed in cold fixative overnight. Several 1 mm^3 samples of the right parietal cortex were dissected, rinsed in phosphate buffer, postfixed in 1% osmium tetroxide, dehydrated through a graded series of ethanol and propylene oxide and embedded in Embed (Electron Microscopy Sciences, Fort Washington, PA). Ultrathin sections were stained with lead citrate and uranyl acetate, and coded specimens were examined using either a Hitachi 11E or a Philips 300 transmission electron microscope at 75 kV or 60 kV, respectively.

RESULTS

Control mice

The vast majority of neurons, their processes and glial cells appeared normal in control mice. A careful search revealed several scattered dilated and swollen astrocytic processes and somata, located primarily around otherwise normal-appearing blood vessels. Swollen dendrites showing a decrease of subcellular organelles, as well as dendrites containing accumulations of normal organelles (mostly mitochondria), were occasionally found. Several types of paracrystalline intranuclear inclusions were observed, the most frequent being fibrillary inclusions, less often paracrystalline rods and lattices. The lattices rarely formed ring-like structures. Small membrane-bound vacuoles or vesicles were found in nuclei of several neurons (fig. 1).

CJD virus-infected mice

Swollen and dilated astrocytic processes were found with approximately the same frequency as in control mice 2 wks postinoculation (Table). Accumulations of normal subcellular organelles, particularly mitochondria and microtubules, were found in a few neurons and dendrites. Occasionally, myelinated axons or dendrites contained membrane-bound electron-dense bodies, and a few axons contained homogeneous electron-dense material, sometimes divided into compartments by membranous septae.

Similar neuropathological changes were seen at 3–12 wks postinoculation (*see* Table). Swollen astrocytic processes and dystrophic axons and dendrites were found. A network of interwoven filaments was found in a single dendrite. Intranuclear vacuoles were

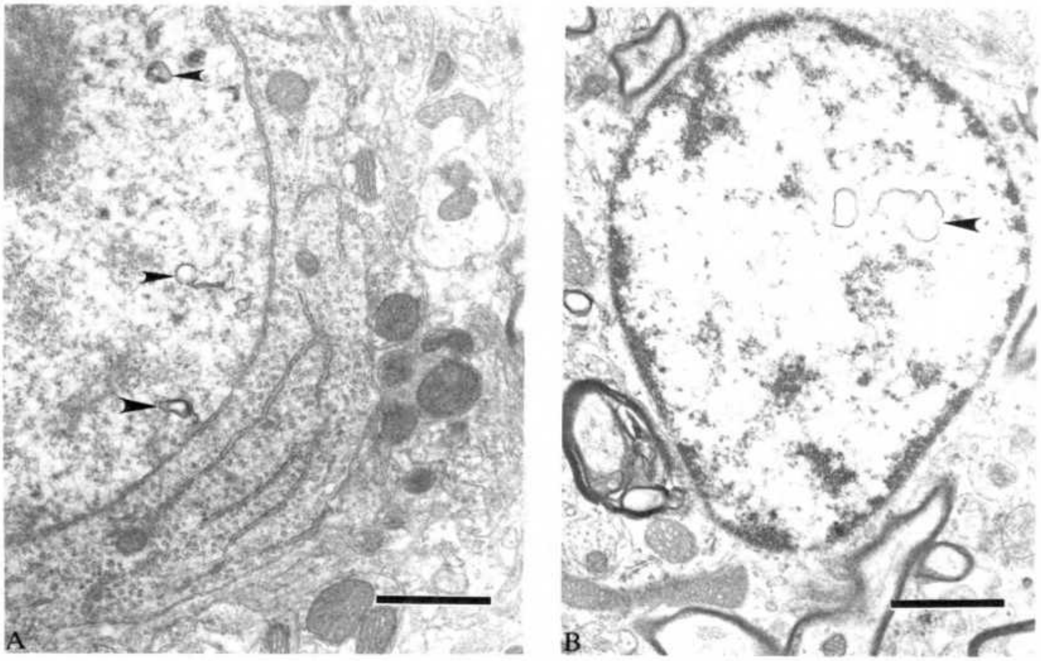

FIG. 1. Intranuclear vacuoles (arrowheads) in parietal cortical neuron of (A) control mouse 7 wks after intracerebral inoculation with saline and of (B) CJD virus-infected mouse 2 wks after intracerebral inoculation. Bar = 1 μm.

TABLE. SERIAL ULTRASTRUCTURAL NEUROPATHOLOGY OF MICE INOCULATED INTRACEREBRALLY WITH THE FUJISAKI STRAIN OF CREUTZFELDT-JAKOB DISEASE VIRUS*

Weeks postinoculation	*Dystrophic neurites*	*Astrocytosis*	*Intranuclear vacuoles*	*Unmyelinated vacuoles*	*Myelinated vacuoles*	*Macrophages*
1	+	+	+	–	–	–
2	+	+	+	–	–	–
3	+	+	+	–	–	–
4	+	+	+	–	–	–
5	+	+	+	–	–	–
6	+	+	+	–	–	–
7	+	+	+	–	–	–
8	+	+	+	–	–	–
9	+	+	+	–	–	–
10	+	+	+	–	–	–
11	+	+	+	–	–	–
12	+	+	+	–	–	–
13	+	+	+	+	+	+
14	++	++	+	++	++	++
16	++	++	+	++	++	++
18	+++	+++	+	+++	+++	+++

* Neuropathological findings in right parietal cortex were graded as: – = none, + = mild, ++ = moderate, +++ = severe. A few dystrophic neurites, mild astrocytosis and rare intranuclear vacuoles were observed in control mice from 2 to 18 wks after intracerebral inoculation with saline. Macrophages and myelinated and unmyelinated vacuoles were not found in control mice.

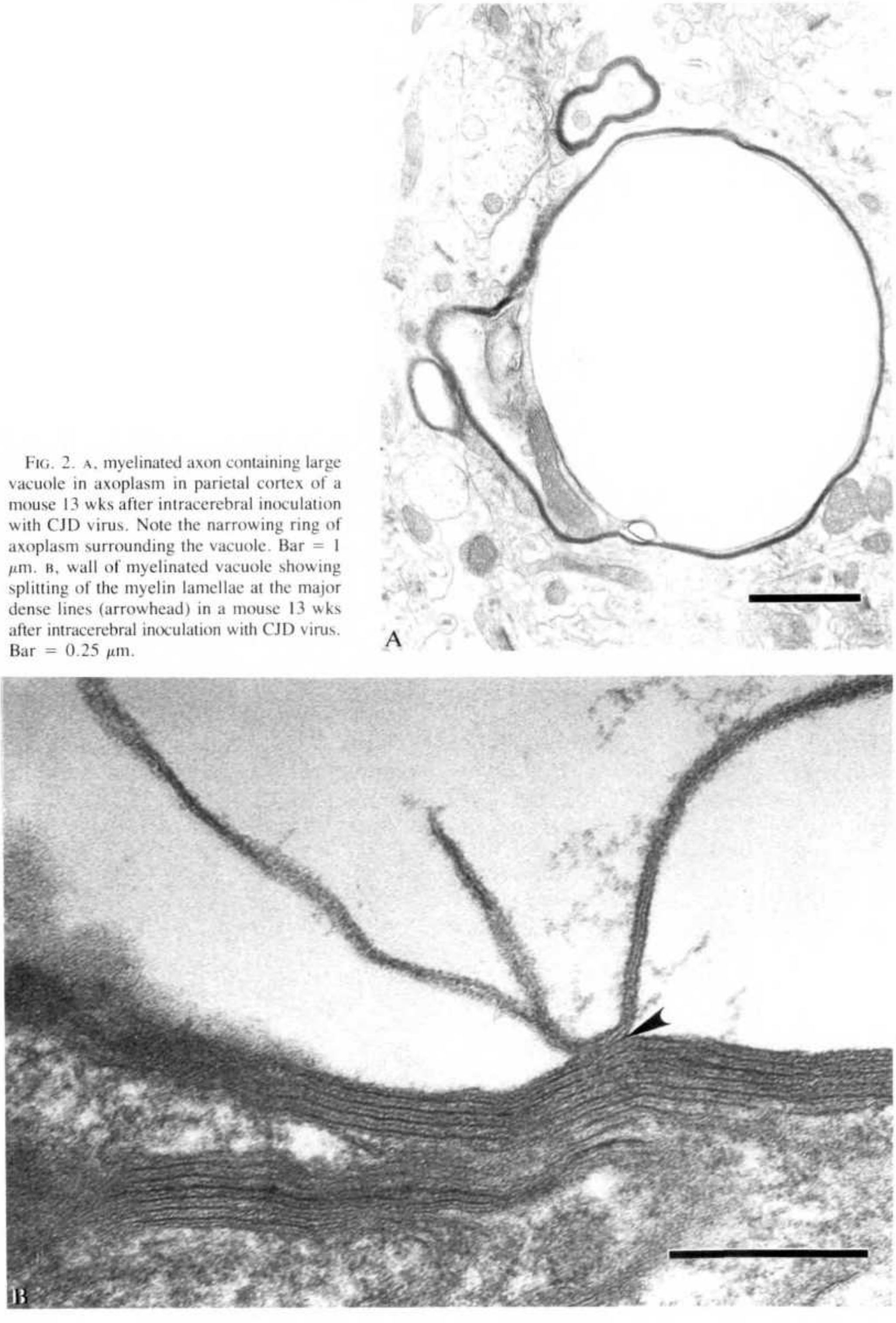

FIG. 2. A, myelinated axon containing large vacuole in axoplasm in parietal cortex of a mouse 13 wks after intracerebral inoculation with CJD virus. Note the narrowing ring of axoplasm surrounding the vacuole. Bar = 1 μm. B, wall of myelinated vacuole showing splitting of the myelin lamellae at the major dense lines (arrowhead) in a mouse 13 wks after intracerebral inoculation with CJD virus. Bar = 0.25 μm.

observed in neurons of CJD virus-infected mice with the same frequency as in control mice (fig. 1).

Spongiform changes were first observed 13 wks after inoculation. Two distinct types of abnormal vacuoles were found. The first type, developing within myelinated axons and thus designated 'myelinated vacuoles' (fig. 2A, B), contained secondary vacuoles (that is, vacuoles within other vacuoles), vesicles, and occasionally, curled membrane fragments. They were seen either within the axoplasm or the myelin sheath which was split either at the major dense line or at the intraperiod line (fig. 2B). These vacuoles were sometimes ensheathed both by astrocyte and macrophage processes, suggesting that they were being digested by these cells. The second type of abnormal vacuole was found within processes not ensheathed in myelin processes (fig. 3) and were designated 'unmyelinated vacuoles'. They were membrane-bound and in neuronal elements, but whether they originated in dendrites or in axonal terminals or preterminals was not always possible to determine. Many more secondary vacuoles, vesicles and curled membrane

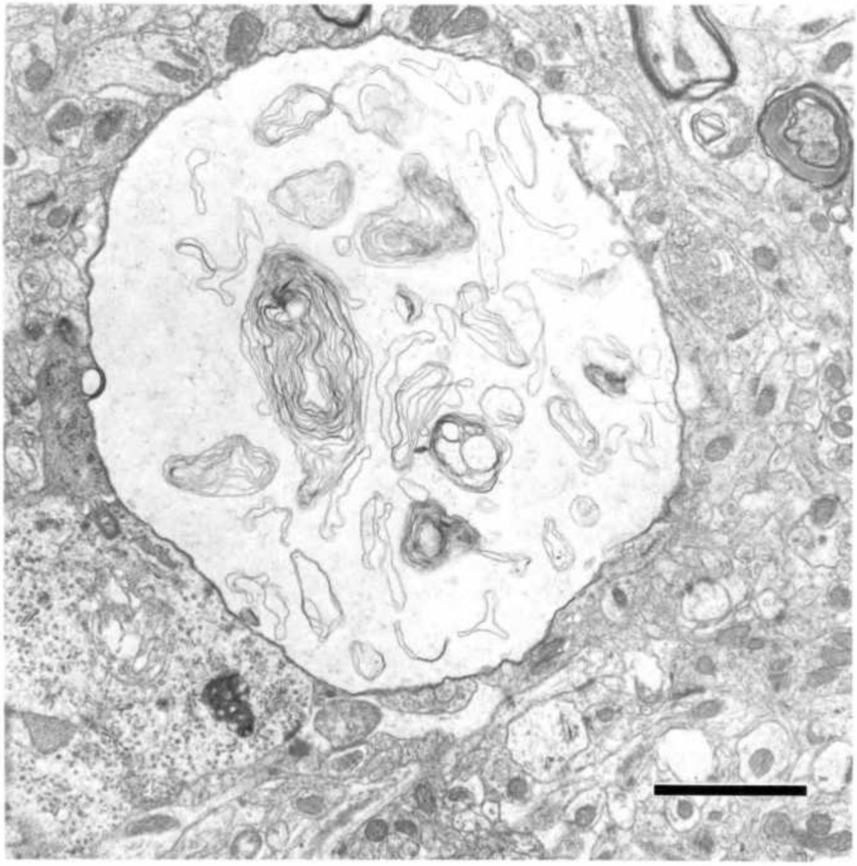

FIG. 3. Large vacuole within unidentified process of a mouse 13 wks after intracerebral inoculation with CJD virus. Note the abundance of secondary vacuoles and disruption of plasma membranes. Bar = 1 μm.

fragments were found within unmyelinated than in myelinated vacuoles. Occasionally vesicular myelin degeneration was observed, and phagocytes seemed to take an active part in the myelin damage. Interestingly, several axons were divided by membranous septae and wrapped in a common myelin sheath, suggesting that there had been faulty remyelination.

Fourteen wks after inoculation, the pathological changes were basically unchanged from those at earlier stages but were more widespread. Some vacuoles were of enormous size and their membranes were frequently discontinuous. Dystrophic neurites containing pleomorphic membrane-bound inclusions were frequently observed.

The ultrastructural pathology characteristic of fully developed CJD emerged 16 wks postinoculation. Numerous vacuoles within myelinated and unmyelinated neuronal processes dominated the pathological picture. Large vacuoles had presumably developed by coalescence of smaller vacuoles. Dystrophic neurites, as well as degenerated axons, contained homogeneous electron-dense material. Swollen astrocyte processes were numerous, but they did not contain abundant glial fibrils (Liberski, 1986*b*, 1987*b*, *c*). Binucleate neurons, resembling these found in kuru-affected chimpanzees (Beck *et al.*, 1975), were observed rarely at this stage (fig. 4).

The first clinical signs of CJD were observed 18 wks postinoculation. Animals exhibited

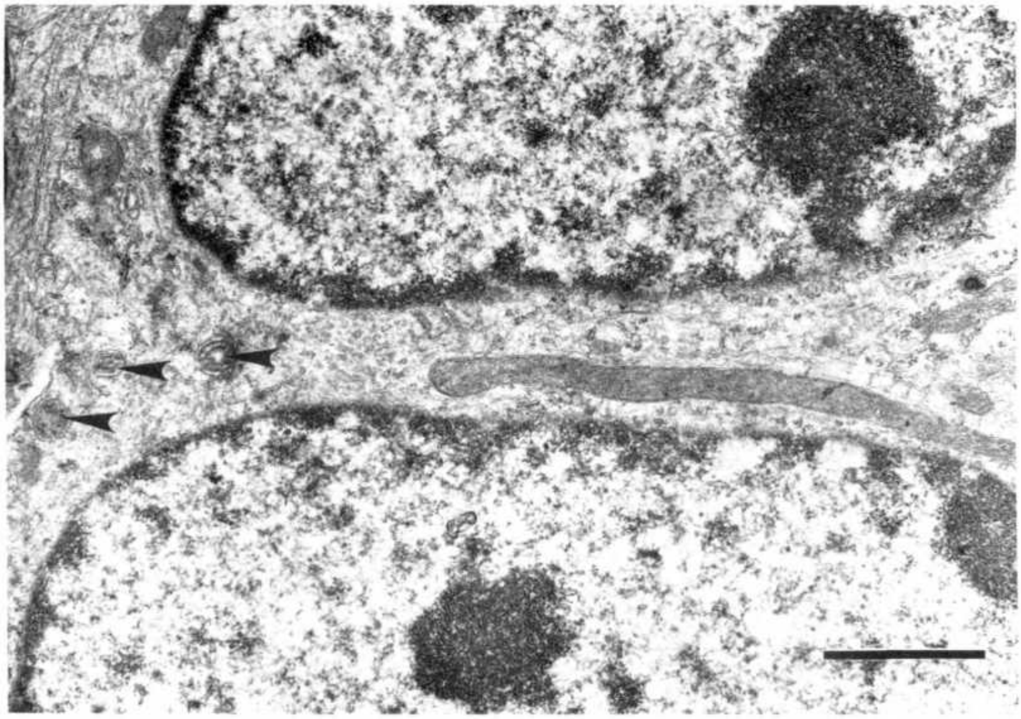

FIG. 4. Binucleated neuron in the parietal cortex of a mouse infected with CJD virus 16 wks postinoculation. Note the cross-sections of centrioles (arrowheads). Bar = 1 μm.

ruffled fur covered with urine and faeces and were rigid, slow and inactive, with delayed responses to external stimuli. They often had a 'plastic tail' (Tateishi *et al.*, 1980). The ultrastructural changes were not qualitatively different from those observed at earlier stages, but they were quantitatively more striking. Both myelinated and unmyelinated vacuoles dominated the picture (figs 2, 3). They were always membrane-bound, usually with disrupted limiting membranes. Large numbers of secondary vacuoles, vesicles, myelin figures, and curled membranes were seen. Some membrane fragments seemed 'fluffy', presumably when cut obliquely. Myelin-bound vacuoles were frequently observed, and the myelin was split at the major dense or intraperiod lines.

Myelinated vacuoles were accompanied by an exuberant cellular reaction comprised of macrophages containing numerous mitochondria, abundant rough endoplasmic reticulum, and secondary lysosomes filled with digested myelin debris, electron-dense material, and myelin-bound vacuoles (fig. 5). Astrocytes and their processes were prominent, with myriad glial fibrils and many mitochondria. Occasionally, double nuclei

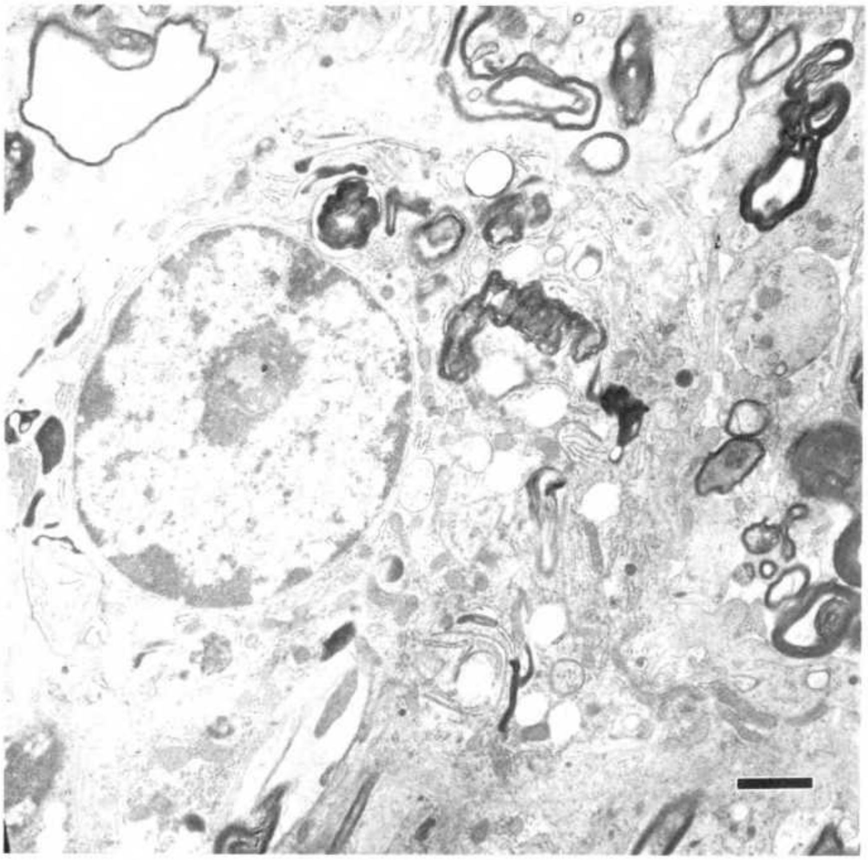

FIG. 5. Macrophage containing lipid droplets and abundant myelin debris in parietal cortex of a CJD virus-infected mouse 18 wks postinoculation. Bar = 1 μm.

in astrocytes were noted, but mitotic figures were never observed. In some areas interwoven astrocyte processes formed a meshwork around other cellular elements and sometimes replaced them.

Neuroaxonal dystrophy was a prominent finding. Several different types of dystrophic neurites were recognized. These were classified according to previously published criteria (Lampert, 1967; Liberski, 1986*a*, 1987*a*; Liberski *et al.* 1989*a*). The first type contained numerous pleomorphic membrane-bound inclusions (fig. 6A, B). Sometimes dystrophic neurites were divided into separate compartments containing membrane-bound bodies (fig. 6C). The second type contained abundant neurofilaments (fig. 6D) in which pleomorphic electron-dense inclusions were enmeshed. The third type contained numerous electron-lucent cisterns and small vesicles. In several areas dystrophic neurites formed small clusters that intermingled with abundant glial processes, presumably representing the earliest stages of neuritic plaque formation (fig. 7). Coiled filaments, indistinguishable from those of Hirano bodies, were found in a few neurons.

DISCUSSION

Development of lesions

In detailed ultrastructural studies of the pathology of CJD in guinea pigs and hamsters (Kim and Manuelidis, 1983*a*, *b*, 1986), swollen astrocyte processes and dendrites, accumulations of otherwise normal subcellular organelles in neuronal processes, and small membrane-bound vacuoles in some neuronal nuclei, encountered as early as 4 wks postinoculation (Kim and Manuelidis, 1986), were regarded as pathological changes. The authors postulated that these abnormal structures accumulated during the incubation period, eventually leading to a complete picture of the fully developed degenerative disease. Such an interpretation implies that the CJD virus replicates slowly in the brain of the host, and this replication is followed by a slow increase in pathological lesions (Eklund *et al.*, 1965). Such a pathogenetic concept of slow virus infections has been challenged recently (Czub *et al.*, 1986). Our morphological data seem more consistent with the hypothesis that spongiform change, the only specific lesion in the subacute spongiform virus encephalopathies (SSVE), develops abruptly and in complete form.

Vacuoles within myelinated and unmyelinated neuronal processes were first detected 13 wks after inoculation, and at later stages the pathology was more severe but not qualitatively different. In other models of SSVE, the fully developed spongiform lesions have been observed at different times: 1.5 months after inoculation with a CJD isolate in pigtail macaques; 2 months after inoculation with either kuru or CJD viruses in sooty mangabeys; 10.5 months after inoculation with a kuru isolate in gibbons (Masters *et al.*, 1976); and 4 months after inoculation with kuru virus in a spider monkey (Beck *et al.*, 1975). If we disregard those changes that we consider to be nonspecific, then unequivocal spongiform changes were first seen in guinea pigs at 8 rather than at 4 wks after inoculation (Kim and Manuelidis, 1986).

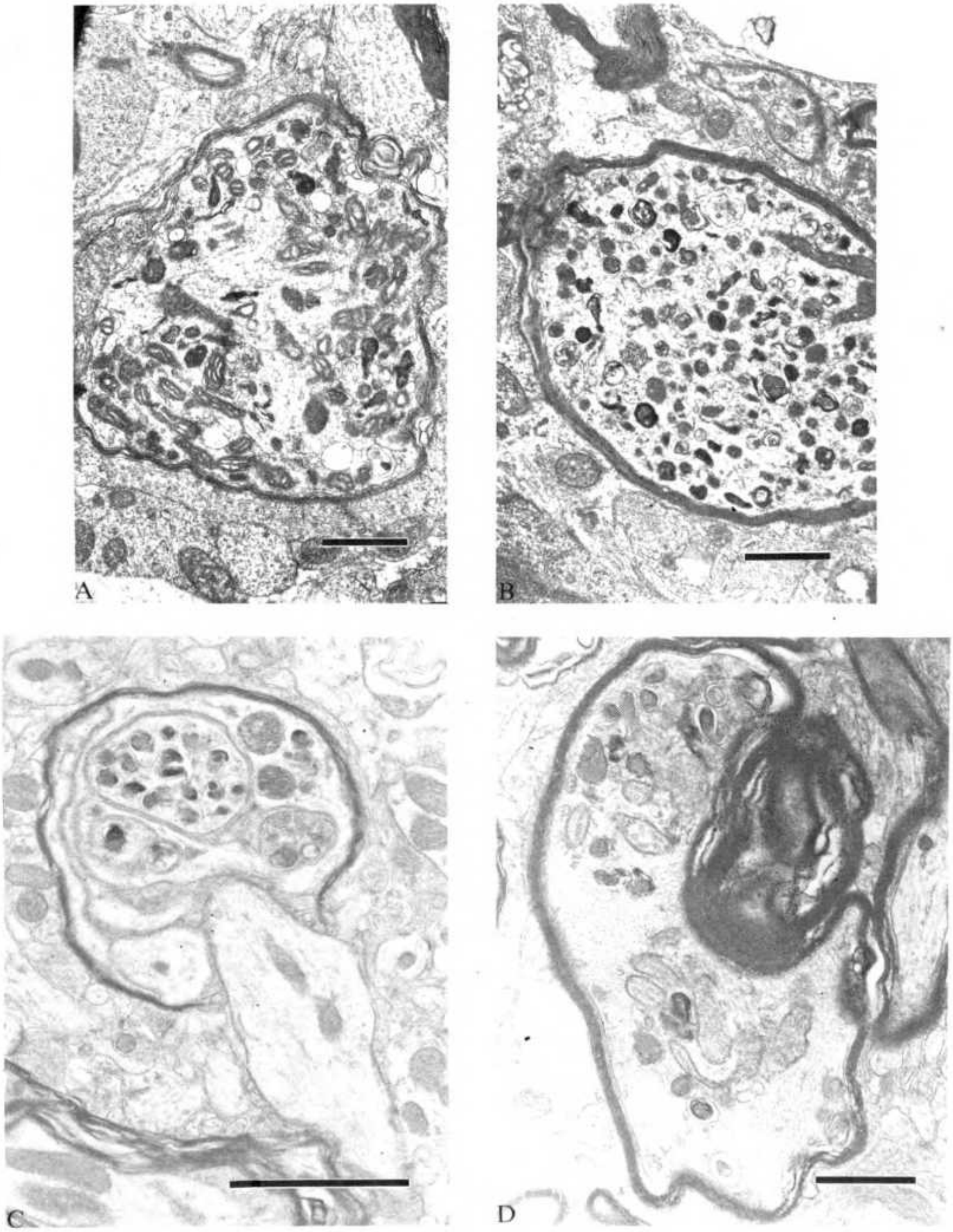

FIG. 6. A, B, myelinated dystrophic neurite containing abundant inclusions (dense bodies) in parietal cortex of CJD virus-infected mouse 18 wks postinoculation. C, cluster of processes wrapped within common myelin sheath in a mouse 18 wks following intracerebral inoculation with CJD virus. Some of these processes appear normal, while others show features of dystrophic neurites. D, myelinated dystrophic neurite containing abundant neurofilaments in parietal cortex of CJD virus-infected mouse 18 wks postinoculation. Note that other subcellular organelles are entrapped within the filamentous masses. Bar = (A, B, C) 1 μm, (D) 0.5 μm.

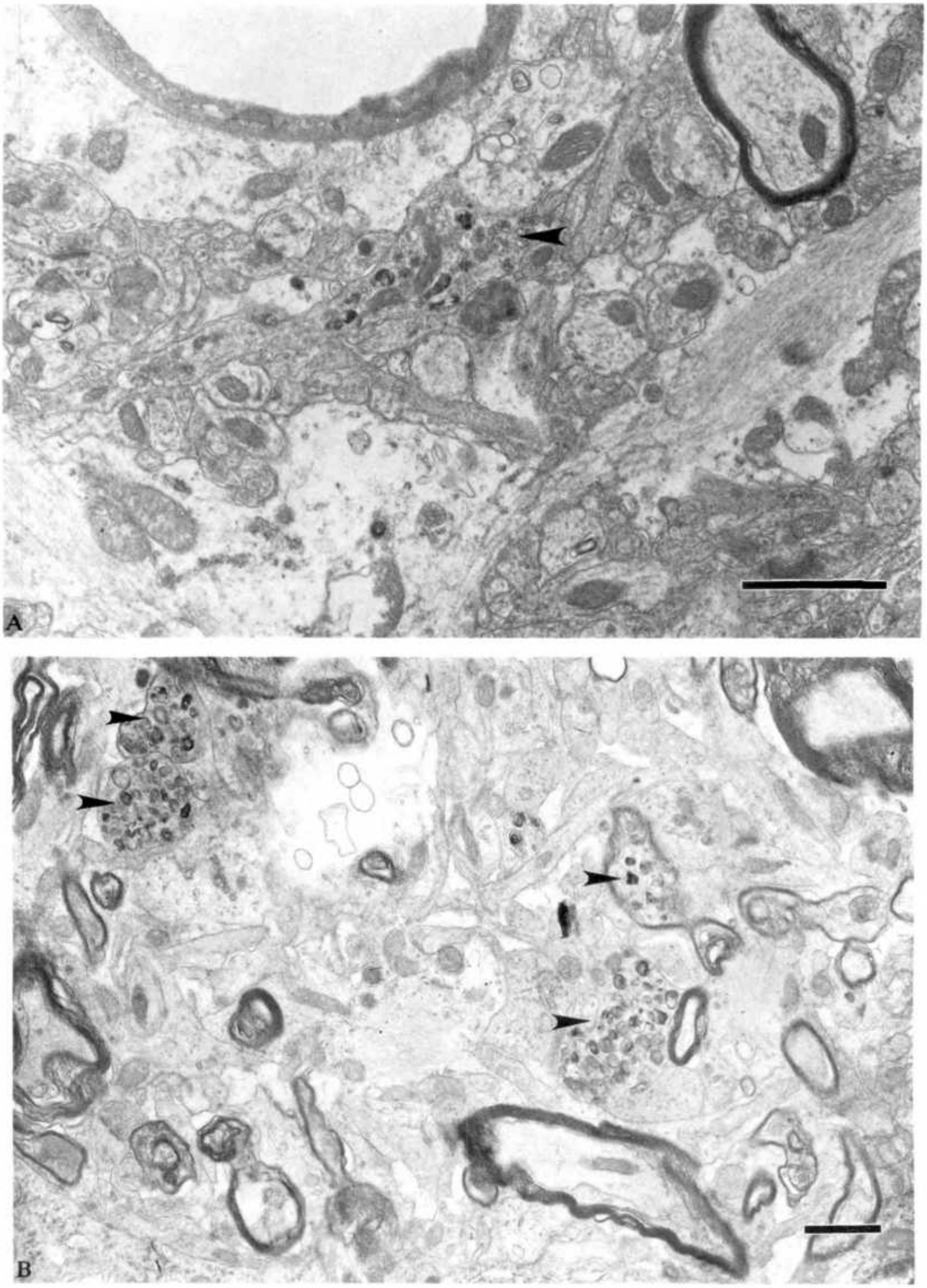

FIG. 7. A, B, small clusters of dystrophic neurites (arrowheads) and abundant astrocytic processes (arrowheads) in parietal cortex of CJD virus-infected mouse 18 wks postinoculation. Bar = 1 μm.

Spongiform changes

Two types of membrane-bound spongiform vacuoles ('myelinated' and 'unmyelinated') were observed as early as 13 wks after inoculation in mice infected with the Fujisaki strain of CJD virus. The cellular elements responsible for the spongiform changes seen at the light microscopical level remain unknown (Fraser, 1976, 1979*a*, *b*, 1981; Masters and Richardson, 1978). Almost every cellular element of the CNS has been implicated. Intracellular vacuoles have been ascribed to astrocyte processes alone (Field and Raine, 1964; Marin and Vial, 1964; Foncin, 1967; Sluga and Seitelberger, 1967), to astrocyte processes and neurons (Gonatas *et al.*, 1965; Kidd, 1967; Brion *et al.*, 1969; Ribadeau-Dumas *et al.*, 1969; Chandler, 1973) and, more recently, to dendrites, axonal terminals and preterminals (Lampert *et al.*, 1969; Bignami and Forno, 1970; Lampert *et al.*, 1971; Bignami and Parry, 1972*a*, *b*; Bubis *et al.*, 1972; Ribadeau-Dumas and Escourolle, 1974; Liberski, 1987*c*). In experimental CJD in guinea pigs and hamsters (Manuelidis and Manuelidis, 1979*a*, *b*; Kim and Manuelidis, 1983*a*, *b*, 1986) the vacuoles have been ascribed almost exclusively to neuronal elements (mostly dendrites), and our study strongly supports that interpretation. Earlier studies showing vacuoles in astrocytes suffered from suboptimal fixation which itself causes swelling of astrocytes.

Intranuclear vacuoles

Intranuclear vacuoles or membrane-bound vesicles, described in CJD by Kim and Manuelidis (1983*a*, *b*, 1986) and later by Cervos-Navarro *et al.* (1986), were found both in control and CJD virus-infected mice. Since they did not increase in size or number, even during the clinical stage of illness, we believe them to be nonspecific changes.

Axonal pathology

Infection with the Fujisaki strain of CJD virus is associated with widespread pathology of myelinated axons accompanied by an intense macrophage reaction (Sato *et al.*, 1980; Tateishi *et al.*, 1983; Liberski *et al.*, 1989*b*). At the ultrastructural level, vacuoles were found within the axoplasm or myelin lamellae, and myelin debris was observed in the cytoplasm of macrophages infiltrating the brain tissues. We also observed myelinated axons and even myelinated vacuoles ensheathed by astrocyte or macrophage cytoplasm (*see* below), and occasionally macrophage processes seemed to penetrate between myelin lamellae. The formation of intramyelin vacuoles is nonspecific and has been observed previously under other pathological circumstances, more often as a result of splitting of myelin at the intraperiod lines as in mice intoxicated with cuprizone (Hemm *et al.*, 1971) or sodium cyanate (Tellez-Nagel *et al.*, 1977), in Rhesus monkeys with vitamin B_{12} deficiency (Agamanolis *et al.*, 1978), in mice with Semliki Forest virus infection (Sheahan *et al.*, 1981) and in sheep with visna (Georgsson *et al.*, 1982). Furthermore, when cultures of mammalian peripheral nerve cells are exposed to a lethal dose of sodium cyanide, myelin splitting is first observed at the intraperiod line and later at the major dense line (Masurovsky and Bunge, 1971). Hence these two mechanisms of vacuole formation may not be mutually exclusive.

This pattern of myelin and axonal pathology also resembles, at least in part, that found in experimental allergic encephalomyelitis (EAE), multiple sclerosis (Raine, 1978, 1984) and the secondary demyelination that follows widespread axonal damage (Lampert and Cressman, 1966). While the white matter damage in experimental CJD differed markedly from that in EAE and multiple sclerosis, which are characterized by marked infiltration of white matter with both mononuclear and polymorphonuclear cells, they share common features: the presence of intramyelin vacuoles, macrophages filled with myelin debris and abundant lipid droplets, and penetration of macrophage processes between myelin lamellae, an especially striking finding in EAE (Bunge *et al.*, 1960; Gonatas *et al.*, 1964; Field and Raine, 1966, 1969; Prineas *et al.*, 1969; Raine *et al.*, 1980; Goban *et al.*, 1986). A plausible interpretation of these similarities is that the mechanism of myelin and axonal pathology may be common to some demyelinated diseases and CJD, regardless of cause.

Neuroaxonal dystrophy

Neuroaxonal dystrophy forms an important part of the ultrastructural picture of CJD. It probably results from the impairment of axoplasmic transport (Dustin and Flament-Durand, 1982). Previously regarded as a nonspecific degenerative phenomenon (Seitelberger, 1971, 1986; Jellinger, 1973), it has been recently reevaluated as an important part of the neuronal degeneration in SSVE (Liberski, 1986*a*, 1987*a*; Liberski *et al.*, 1989*a*; Gibson and Liberski, 1987). It is a well-known form of neuronal degeneration of numerous pathological conditions both of the central and peripheral nervous systems, as well as in otherwise normal mammalian brains (Jellinger, 1973; Liberski, 1986*a*, 1987*a*; Liberski *et al.*, 1989*a*). The ultrastructure of dystrophic neurites, which form the substrate for neuroaxonal dystrophy, is indistinguishable in pathological and nonpathological states (Jellinger, 1973), but are much more abundant in the former (Jellinger, 1973; Liberski *et al.*, 1989*a*; Gibson and Liberski, 1987). Dystrophic neurites, filled with pleomorphic inclusions, are probably identical to the reactive axonal enlargements reported by Lampert (1967), who reserved the term dystrophic neurites for structures filled with branching tubules and proliferating plasma membranes. However, both subcategories of abnormal axons overlap, and they form only the extreme ends of a spectrum (Jellinger, 1973; Yagihashi and Sima, 1986; Liberski *et al.*, 1989*a*).

The significance of neuroaxonal dystrophy in SSVE is unclear. It appears relatively early in the incubation period; for example, in mice infected with the 22C or 79A strains of scrapie virus, vacuolation in the CA1 region of the hippocampus precedes the increase in dystrophic neurites, while in mice infected with the ME7 strain, vacuolation follows the increase in these neurites (Gibson and Liberski, 1987). Isolated dystrophic neurites were found in mice as early as 2 wks after inoculation with the Fukisaki strain of CJD virus. Increased numbers were observed some 11 wks later, approximately when vacuoles were first found. Hence, neuroaxonal dystrophy and vacuolation probably evolve independently. It is plausible that neuroaxonal dystrophy is an ultrastructural marker for the depopulation of neurons. It seems to be widespread throughout the brain in SSVE and is not confined to the gracile and cuneate nuclei, as first reported (Jellinger, 1973).

Several hypotheses have been proposed to explain the accumulation of abnormal organelles in dystrophic neurites (for a review, *see* Jellinger, 1973). As recently proposed, impairment of slow axonal transport may be a final common pathogenetic pathway in SSVE, senile dementia of Alzheimer type (SDAT) and motor neuron disease (Gajdusek, 1985). Interference with slow axonal transport is directly responsible for the formation of axonal spheroids in ligated sciatic nerve (Griffin *et al.*, 1977), in acrylamide polyneuropathy (Pleasure *et al.*, 1969) and in transsected spinal cord axons (Kao *et al.*, 1977). We conclude that nearly identical patterns of neuronal degeneration result, regardless of the cause.

Perhaps the most important problem that remains to be settled is the association between dystrophic neurites and the formation of neuritic plaques. The neuritic plaques of SSVE and of SDAT are composed of dystrophic neurites, ultrastructurally indistinguishable from those described here (Lampert, 1971; Wiśniewski and Terry, 1973; Wiśniewski *et al.*, 1975; Bruce and Fraser, 1975; Masters *et al.*, 1981). Small clusters of such neurites probably constitute the 'immature' neuritic plaques found in SDAT (Wiśniewski *et al.*, 1981) and in experimental scrapie (Fukatsu *et al.*, 1984; Liberski, 1986*a*, 1987*a*). Furthermore, the production of plaques is, at least partially, governed by the strain of scrapie virus (Bruce *et al.*, 1976), but not by the age of the host (Bruce and Fraser, 1982). However, the number of dystrophic neurites found in mice infected with plaque- and nonplaque-producing strains of scrapie virus is approximately the same (Gibson and Liberski, 1987). That 'neuritic' and 'amyloid' plaques, despite their morphological similarities, may have different origins must also be considered (Gibson, 1985).

In both CJD and SDAT the amyloids are modified proteins of unknown function (Prusiner *et al.*, 1983; Oesch *et al.*, 1985; Wong *et al.*, 1985; Goldgaber *et al.*, 1987). Antibodies against PrP proteins stain the amyloid plaques in SSVE (Bendheim *et al.*, 1984; DeArmond *et al.*, 1985). Because the smallest neuritic plaques are composed exclusively of dystrophic neurites without any amyloid fibrils (Wiśniewski *et al.*, 1981; Fukatsu *et al.*, 1984; Liberski, 1986*a*, 1987*a*), it is plausible that clusters composed of such neurites may act as niduses on which amyloid precursor proteins are processed and later on which amyloid is deposited.

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CEREBELLAR INFARCTION IN THE TERRITORY OF THE ANTERIOR AND INFERIOR CEREBELLAR ARTERY

A CLINICOPATHOLOGICAL STUDY OF 20 CASES

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SUMMARY

Clinicopathological reports on infarction in the territory of the anterior inferior cerebellar artery (AICA) are rare. In the present series cerebellar infarcts involved only the AICA territory in 13 cases. They were bilateral in 3 cases. In these pontocerebellar infarcts the middle cerebellar peduncle was the core of the affected territory. It was seldom selectively affected. In a few cases, the infarction extended to the flocculus. Next most frequently involved was a thin band of tissue in the adjacent cerebellar white matter, comprising laterally the neighbouring cerebellar lobules. The largest infarcts extended to the anterior and inferior aspects of the cerebellum. In these cases, the posterior inferior cerebellar artery (PICA) was hypoplastic. In most infarcts, the inferolateral pontine territory was involved, the infarction sometimes extending up to the middle third of the lateral pons and down to the superior part of the lateral medulla. No brainstem compression or tonsillar herniation were observed with infarcts affecting the AICA territory alone. Clinically, involvement of several cranial nerves (facial palsy, multimodal trigeminal sensory impairment, deafness, sometimes with tinnitus, a vestibular syndrome, or lateral gaze palsy) was constant. Cerebellar signs and motor weakness occurred frequently. Contralateral pain and temperature sensory loss was present at times. Horner's syndrome or skew deviation was rare. Study of the arteries showed that arterial occlusion was mainly due to thrombosis superimposed on atheromatous stenosis. In 7 cases, the infarction also involved the PICA territory or the PICA and the superior cerebellar artery territories. These extensive infarcts were often associated with tonsillar herniation and massive paramedian brainstem infarction. The cases in which the territories of the three cerebellar arteries were affected presented in deep coma, together with tetraplegia in some patients. Those in which PICA and AICA territories were involved together presented with similar clinical features as in the cases in which only the AICA territory was involved.

INTRODUCTION

Few detailed clinicopathological observations on isolated infarction in the territory of the anterior inferior cerebellar artery (AICA) are available. Goodhart and Davison (1936) gave the first pathological description of a case of AICA occlusion, unexpectedly discovered at autopsy in a 47-yr-old woman who had had an episode of vertigo, vomiting and occipital headaches 8 yrs earlier, unexplained at the time. Adams (1943) described fully a clinicopathological case. The 'syndrome of the anterior inferior cerebellar artery'

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is based on this latter description which has remained unique in the literature up to the present. The 7 cases reported by Atkinson (1949) did not make it possible to define the AICA syndrome. During neurosurgical removal of acoustic neurinomas, clipping of the AICA led to coma and death in 6 cases; pathological findings included infarction, sometimes haemorrhagic, or 'laceration' and 'pontine malacia', located in the territory supplied by the AICA. Guillain *et al.* (1929) reported a single case of cerebellar infarction involving the whole of the middle cerebellar peduncle and some of the inferior portion of the hemisphere. This case can be attributed retrospectively to occlusion of the AICA from the current anatomical data. Silverstein (1972) briefly reported 2 clinicopathological cases. Major reviews on the vascular disorders of the brain do not mention additional case reports (Foix and Hillemand, 1926; Lhermitte and Trelles, 1934; Trelles, 1935; Kubik and Adams, 1946; Biemond, 1951; Cannon, 1951; Gillilan, 1964; Stehbens, 1972; Garcia, 1985; Graham and Brierley, 1984; Toole, 1984; Zülch, 1985; Pou-Serradel, 1987). We have performed a retrospective clinicopathological study of 20 cases with cerebellar infarction in the AICA territory.

ANATOMY

Course

The anterior inferior cerebellar artery is an almost constant artery. According to Lazorthes (1961) it is absent in only 4% of individuals. The point where it originates is variable, and often differs from one side to the other. The artery usually arises from the basilar artery, from the lower third in 75% of cases, sometimes from the middle third, and occasionally from its lower limit (Stopford, 1915–1916). However, it can arise from the vertebral artery or the basilar artery by a common trunk, together with the posterior inferior cerebellar artery (PICA). Rarely, it is replaced by several small vessels arising directly from the basilar artery or from the internal auditory artery. The artery passes laterally, posteriorly and inferiorly below the fifth nerve, crosses the sixth nerve, and then reaches the cerebellopontine angle where it meets the acousticofacial bundle. Where it crosses the eighth nerve, after having given rise to the internal auditory artery, it divides into two branches (Atkinson, 1949), one of which travels laterally and downwards towards the anterior inferior part of the cerebellum. The other branch travels laterally and horizontally, making a loop around the acousticofacial bundle and reaches the flocculus, the middle cerebellar peduncle, and the mid part of the cerebellar hemisphere, giving rise to branches to these structures and to the adjacent part of the pons. Before dividing, the principal trunk gives rise to small vessels that reach the lateral part of the pons, from the junction of its superior and middle thirds to the superior third of the lateral part of the medulla. There are thus two distinct brainstem territories: the proximal trunk supplies the lateral part of the pons and the lateral branch supplies both the middle cerebellar peduncle and the tegmental portion of the inferior two-thirds of the pons.

Distribution

The cerebellum. The cerebellar territory supplied by the AICA varies as a function of its calibre, which is usually asymmetric. Nearly always the artery supplies the flocculus, the only region of the cerebellum usually vascularized solely by the AICA (Lazorthes, 1961), except in 3–5% of individuals where the AICA is replaced by the PICA. In 40% of subjects the AICA ends on the flocculus (Lazorthes, 1961). In others, it follows the sulcus separating the anterior lobes and the lobulus semilunaris and gives rise to terminal branches that supply the neighbouring lobules: anterior, simplex, semilunaris superior, semilunaris inferior, gracilis, and biventer in 18% (Lazorthes, 1961) to 50% of subjects (Takahashi *et al.*, 1968). The AICA can replace a hypoplastic PICA, taking over most of the inferior surface of the cerebellum including the anterolateral part of the tonsillar lobe except for the vermis. According to Stopford (1915–1916), Foix and Hillemand (1925), Atkinson (1949) and Takahashi (1974), there is a balance in size between the AICA and the PICA. The terminal branches of the AICA anastomose with the SCA and the PICA at the border zone areas.

The pons. The pontine distribution of the AICA has been precisely described by Duvernoy (1978). Two kinds of branches participate. *Descending branches* penetrate the pons at or just above the medullopontine sulcus. Some of these branches may constitute the superior and the posterior rami of the lateral area of the medulla, supplying the fibres of the ninth and tenth nerves and the superior part of the nucleus ambiguus (Duvernoy, 1978). The other branches have a central course towards the lower limit of the pontine tegmentum, where they supply a well-defined territory, the lateral region of the pons (Adams, 1943; Duvernoy, 1978) (fig. 1). This includes the superior olivary nucleus, the facial nucleus, the lateral lemniscus, the anterolateral tract (spinothalamic tract), the spinal trigeminal tract and its nucleus, the superior, lateral and median vestibular nuclei, the trapezoid body, the cochlear nucleus and, in some cases (Duvernoy, 1978), the lateral part of abducens nucleus and the central tegmental tracts. Lastly, some of these rami cover and supply the middle cerebellar peduncle. *Ascending branches* often reach the trigeminal nerve. Some of these rami penetrate its root and, together with the lateropontine artery, follow the nerve to supply the principal sensory nucleus (Duvernoy, 1978). Some others supply the superior vestibular nucleus. In the proximity of the trigeminal root, some rami anastomose with the inferior lateropontine artery, which supplies the anterior area of the lateropontine territory. This latter artery sometimes arises from AICA, so that the territory of the inferior lateropontine artery can be part of the distribution of the AICA. Some rami sometimes pass behind the trigeminal root, where they anastomose with the superior lateropontine artery (a branch of the SCA), making an arterial circle that surrounds the trigeminal root, or sometimes only its sensory root (Duvernoy, 1978).

The AICA thus supplies the middle cerebellar peduncle in every instance, the lower third of the lateropontine territory in most, its middle third frequently and, in a few individuals, the superior part of the lateral region of the medulla.

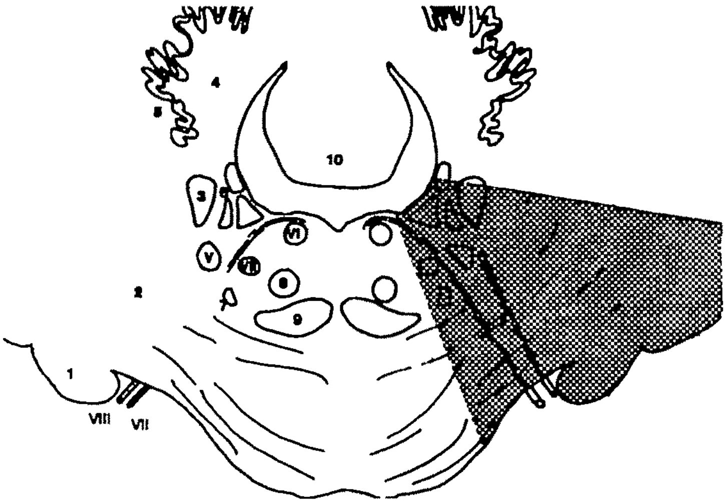

FIG. 1. Anatomical drawing of the territory supplied by the AICA on section through the nucleus of the sixth nerve, involving the lateral pontine territory, the middle cerebellar peduncle, the flocculus and the anterior part of the cerebellar lobules. 1 = flocculus; 2 = middle cerebellar peduncle; 3 = inferior cerebellar peduncle; 4 = superior cerebellar peduncle; 5 = dentate nucleus; 6 = superior, lateral and medial vestibular nuclei; 7 = anterolateral (spinothalamic) tract; 8 = central tegmental tract; 9 = medial lemniscus; 10 = nodulus. (Modifed from Amarenco and Hauw, 1989.)

Two other inconstant cerebellar arteries have been described: the medial and inferior cerebellar artery, arising from the origin of the basilar artery and supplying the flocculus, lobulus biventer and the tonsil, and the lower supplementary cerebellar artery, rising from the basilar artery or from the auditory artery and supplying the anterior surface of the cerebellum (Jakob, 1928; Lazorthes, 1961).

MATERIAL AND METHODS

A total of 162 cases with large cerebellar infarcts (exceeding 2 cm in diameter), who died between January 21, 1963 and April 12, 1982 in the neurological departments of La Salpêtrière Hospital were recorded in the files of the Raymond Escourolle Laboratory of Neuropathology. They represented 1 in 24 of the autopsies carried out during this period (162/3877). Sixty-four cases were selected, based on the following criteria: detailed clinical data, a thorough autopsy with examination of the heart and, in most cases, a thorough study of the arterial supply of the brain, including the cervical segment of the vertebral arteries. A macroscopic and microscopic study of the cerebral hemispheres, the brainstem and the cerebellum, including a systematic analysis of the brainstem structures and of the cerebellar lobules affected by the infarction, were performed in order to identify the arterial territory involved.

Using a method described by Lhermitte *et al.* (1966) and modified by Escourolle (1966), the aorta and its cervical branches were dissected out. In addition, examination of the bony segment of the arteries of the neck and of the skull was performed with 4 exceptions (Cases 3175, 6911, 5192, 3013) by en bloc removal of the cervical spine and the base of the skull and further decalcification. For each case, the arterial configuration and the size and extent of arterial lesions were reconstructed on diagrams. Photographs of the external surfaces of the cerebellum, made before section, were analysed according to figs 333, 340, 342, 348 of Dejerine (1901). After dissection of the blood vessels, en bloc cuts of the brainstem and cerebellum were obtained perpendicular to the axis of the brainstem. For each case, at least 3 different levels of the cerebellum were sampled. They were embedded in celloidin and stained with haematoxylin and eosin, and Loyez haematoxylin for myelin. Levels of section were analysed according to Dejerine's figs 432, 434, 436, 437, and figs 43, 44, 45, and 66 to 77 of Nieuwenhuys *et al.* (1981).

In 20 patients (Cases 3175, 5515, 5934, 5060, 6911, 6863, 6056, 5165, 5192, 6031, 6522, 3013, 6504, 6523, 3964, 5955, 6720, 5901, 5339, 5280) the infarction involved the AICA territory. In 13 cases, it involved only this territory in the cerebellum, whether unilateral or bilateral. In 7 cases, other infarctions affected the SCA and/or PICA territories. Old infarctions, dating from more than 3 months before the autopsy or unexpectedly discovered at autopsy, and recent infarctions were distinguished taking into account clinical and pathological data (Duyckaerts and Hauw, 1985). Cases 3175 and 3013 were included in the study of Hauw *et al.* (1976).

RESULTS

Twenty-four cerebellar infarcts in the AICA territory were studied in 20 patients: 16 of these involved only the AICA territory and 8 the AICA territory together with other cerebellar infarcts in the SCA and/or PICA territory.

Cerebellar infarction involving only AICA territory

There were 13 cases (3 with bilateral infarction) (Table 1). Their mean age (9 male, 6 female) was 68 yrs. Three cases were old infarctions.

Neuropathological findings

There were 16 infarcts (8 left, 2 right, 3 bilateral). The cerebellar structures involved were: middle cerebellar peduncle (16), flocculus (11), lobulus simplex (8), lobulus

TABLE 1. CLINICAL AND PATHOLOGICAL DATA FOR 13 CASES OF CEREBELLAR INFARCTION INVOLVING THE AICA TERRITORY ALONE

		Signs on admission						
Case	*Onset*	*Cerebellar*	*Vestibular*	*Cranial nerve involvement*	*Others*	*Vigilance*	*Pattern of vascular occlusion*	*Pathological findings*
3175	Vertigo, tinnitus, unsteadiness	Dysmetria	Nystagmus	V, VII, hearing loss, dysphagia	Leg weakness, Babinski response			PCM, LPT, flocculus, cerebellum
5515	Vertigo, vomiting, headache facial numbness			V, VI, VII			BA prox. half, VA distal part above PICA ostium	PCM, LPT, MPT, flocculus, cerebellum
5934	Vertigo, dysarthria, transient loss of consciousness unsteadiness	Ataxia	Nystagmus	VII, gaze palsy	Dysarthria, tetraparesis, Babinski response	Somnolence	BA prox. 2/3, VA distal part with PICA ostium	PCM, LPT flocculus
5060	Dysarthria, vomiting, visual field impairment			III × 2, VII, gaze palsy	Dysarthria, hemiplegia, Babinski response	Somnolence		PCM, MMT
6911	Dysarthria, headache, vomiting, unsteadiness	Dysmetria	Nystagmus	Hearing loss, V, VI, VII, skew dev., dysphagia	Dysarthria hemianaesthesia, hemianopia		AICA	PCM, LPT, flocculus, cerebellum
6863	Headache, facial weakness	Dysmetria	Nystagmus	V, VII, gaze palsy, Horner's, dysphagia	Contralat. thermoanalgesia Babinski response		BA prox. half, VA distal part above PICA ostium	PCM, LPT, flocculus
6056	Unsteadiness, facial weakness			V, VII, dysphagia,	Babinski response	Somnolence	VA distal part with AICA ostium	PCM, LPT, flocculus, cerebellum
5165	Dysarthria, vomiting, facial numbness, facial weakness			V, VI, VII	Dysarthria			PCM, LPT, flocculus, cerebellum
5192	Not relevant*			Not relevant*			BA middle in front of AICA ostium	PCM, MPT
6031	Vertigo, hiccup, unsteadiness, somnolence		Nystagmus	VII, gaze palsy, hearing loss			VA bilat. distal above, PICA ostium	PCM, LPT, MPT, MMT, flocculus, cerebellum
6522	Vertigo, vomiting, headache			VII, dysphagia	Contralat. thermoanalgesia, ipsilat. hemiplegia		BA proximal half	PCM, LPT, MPT, MMT, cerebellum
3013	Vertigo, hemiplegia, transient loss of consciousness somnolence	Dysmetria		V, gaze palsy, dysphagia	Contralat. thermoanalgesia	Somnolence	VA bilat. distal above PICA ostium	PCM, LPT, MMT, flocculus, cerebellum
6504	Vertigo, vomiting, headache, tinnitus, somnolence	Dysmetria	Nystagmus	Tinnitus	Ipsilat. arm weakness	Somnolence	VA distal part above PICA ostium	PCM, LPT, MMT, cerebellum, thalamus, occipital lobe

* Case with a massive associated infarct in the territory of the middle cerebral artery with symptoms and signs overshadowing those related to AICA occlusion. PCM = pedunculus cerebellaris medius; LPT = lateral pontine territory; MPT = median pontine territory; MMT = median mesencephalic territory; BA = basilar artery; VA = vertebral artery; AICA = anterior inferior cerebellar artery; PICA = posterior inferior cerebellar artery.

semilunaris superior (6), lobulus semilunaris inferior (10), lobulus gracilis (8), lobulus biventer (7), tonsil (2). The anterior lobe was never affected. The anterior part of the dentate nucleus was very mildly involved in 3 instances. The vermis was not affected, except for 1 case (3013) with bilateral infarction in AICA territory, involving the culmen, the tuber, and the pyramis. In 1 case (5192), the flocculus could not be studied. The cerebellar lobules were affected in their anterior and lateral portions and very rarely posteriorly (Case 3013). The cerebellar lesions were restricted in 2 cases to the middle cerebellar peduncle (5060, 5192). The flocculus was also involved twice (5934, 6863). The infarct involved the middle cerebellar peduncle and the flocculus and the lesion extended laterally into the neighbouring cerebellar lobules, located between the territories of the SCA and PICA, 6 times (3175, 5515dr, 5515g, 5165, 6031dr, 6031g). The lesion extended into a large portion of the caudal part of the cerebellar hemisphere 6 times (6911, 6056, 6522, 3013dr, 3013g, 6504). This occurred when a large AICA had taken over the usual territory of the lateral branch of the PICA.

Associated infarction of the brainstem was observed in the territory of the lateral arterial group of the inferior and the middle thirds of the pons (usually supplied by the AICA) in 13 infarcts out of 16. In 3 other infarcts, the lesion was smaller in size, but involved at least the middle cerebellar peduncle. The structures involved were as follows: the trigeminal nerve in 13 infarcts out of 16 (trigeminal nucleus 6; spinal trigeminal tract 8; trigeminal fibres 4), the facial nerve in 12 infarcts (fibres 12; nucleus 5), the vestibular nuclei (10), the acoustic structures in 9 infarcts (fibres 8; cochlear nucleus 1; trapezoid body 5; lateral lemniscus 2), the anterolateral (spinothalamic) tract (9), the lateral reticular nucleus (5), and the corticotegmental tract, the spinal nucleus of the glossopharyngeal nerve and the fibres of this nerve, the fibres of the abducens nerve, each in 1 case. The nucleus of abducens nerve was never involved. The infarction occasionally involved the pontomedullary junction (Cases 3175, 6863) in the upper part of the lateral and dorsal medullary region.

Brainstem involvement, outside the territory usually supplied by the AICA, and occipital and thalamic infarcts occurred in 9 cases out of 13: an occipital infarct was noted in 4 cases, thalamic infarction in 4 cases, median mesencephalic infarction in 5 cases (frequently extending into the upper regions of the pons: 1 to the anterolateral territory of the upper part of the pons, another to the median territory of the upper part of the pons and to the anterolateral territory of the upper and middle part of the pons, a third extending to the median territory of the upper part of the pons), a median midpontine infarction and a median medullary infarction each in 1 case. One case was associated with infarction in the territory of the middle cerebral artery. Lacunar infarctions were noted in 6 cases, 5 in basal ganglia, 5 in the brainstem, and 6 in the hemisphere white matter.

Vascular studies

Arterial occlusion was observed in 10 cases, 2 of which were located in the distal part of the ipsilateral vertebral artery, 1 rostral to the PICA ostium, the other in front of the origin of the AICA from the vertebral artery. Two others were situated on the distal part of both vertebral arteries (above the PICA ostia). In 4 cases, the occlusion was located in the lower part of the basilar artery (3 of which were associated with an occlusion of the vertebral artery, facing or rostral to the PICA ostium). In 1 case, occlusion of the middle third of the basilar artery had occurred together with AICA occlusion. In the last case, only the AICA was occluded.

The occlusion was embolic in 1 case, without obvious origin. This case was associated with very severe atheroma of the intracranial vessels. Occlusions were due to thrombosis superimposed on atheromatous stenosis in 9 cases, 2 of which were associated with an ectatic basilar artery (5515, 6911) and 1 other with a trigeminal artery (5192). In the 3 cases without occlusion seen at postmortem examination, 1 was associated with embologenic cardiac disease (mitral stenosis with atrial fibrillation), another was associated with very severe diffuse atherosclerosis of intracranial vessels and the third lacked obvious associated aetiological factors.

Retrospective clinical study

Four patients out of 13 had already experienced a stroke. Eight had high blood pressure and 3 had ischaemic heart disease. Two patients had diabetes mellitus and another had hypercholesterolaemia. Clinical data relevant to AICA infarction were available in 12 patients (15 infarctions) (Table 1). In the last case, signs and symptoms were overshadowed by massive infarction in middle cerebral artery territory (5192).

The onset was always sudden. In 2 cases, the stroke was preceded by a transient ischaemic attack. Two other cases had a stepwise course. The initial symptoms were as follows: vertigo, 'dizziness' (7), nausea and vomiting (6), headache (5), unsteadiness (5), dysarthria (4), facial palsy (3), somnolence (3), tinnitus (2), transient loss of consciousness (2), facial numbness (2), and hemiplegia (1).

The first neurological examination on admission mainly showed signs of multiple cranial nerve involvement, cerebellar signs, motor weakness and somnolence, sometimes with a crossed sensory syndrome. Cranial nerve involvement was noted in every case. An average of 3 ± 1 cranial nerves was affected per case. Peripheral facial nerve palsy occurred in 10 cases, trigeminal nerve involvement in 7, nystagmus and dysphagia in 6, lateral gaze palsy or abducens paralysis in 4, deafness and contralateral thermoanalgesia in 3, and Horner's syndrome in 1 case. Cerebellar signs were present in 6 cases, with dysmetria in 5 and ataxia in 1. Motor weakness was oberved in 6 cases: hemiparesis in 3, hemiplegia in 2, and tetraparesis in 1. There was skew deviation in 1 case. Delayed coma occurred in 5 cases, with tetraplegia in 4. Oculomotor palsies and respiratory failure were also noted. Death was due to massive median brainstem infarction in 4 cases, and to infective or thromboembolic complications in 7 cases. Sudden death of undetermined origin occurred in 2 cases.

Multiple infarctions of the cerebellum involving the territory of several cerebellar arteries, including the territory of the AICA

Eight infarcts in the AICA territory (bilateral in 1 case) were observed in 7 cases (Table 2).

TABLE 2. CLINICAL AND PATHOLOGICAL DATA FOR 7 CASES OF CEREBELLAR INFARCTION INVOLVING THE TERRITORY OF SEVERAL CEREBELLAR ARTERIES INCLUDING THE TERRITORY OF THE AICA

		Signs on admission						
Case	*Onset*	*Cerebellar*	*Vestibular*	*Cranial nerve involvement*	*Others*	*Vigilance*	*Pattern of vascular occlusion*	*Pathological findings*
6523	Vertigo, vomiting, facial numbness and weakness	Dysmetria	Nystagmus	Hearing loss, V, VII			VA distal part with ostium of trunk giving rise to AICA and PICA	PCM, LPT, LMT, flocculus, cerebellum
6720	Vertigo, vomiting, hiccup, headache, unsteadiness, facial weakness, tinnitus	Dysmetria		V, VII, skew dev., Horner's syndrome, dysphagia	Hemiparesis, contralat. thermoanalgesia		VA distal part	PCM, LPT, LMT, MPT, MMT, cerebellum
5280	Vertigo, vomiting, headache, tinnitus, unsteadiness	Ataxia	Nystagmus	Hearing loss V, VII			PICA contralateral to the AICA infarct	PCM, flocculus, cerebellum
3964	Vomiting, coma					Deep coma		PCM, flocculus, cerebellum
5955	Somnolence			VII, gaze palsy	Hemiparesis, Babinski response	Coma		PCM, LPT, MMT, cerebellum
5901	Headache, vertigo, vomiting, transient loss of consciousness, blurred vision			V, gaze palsy	Tetraplegia, decerebrate signs, respiratory failure	Deep coma	BA whole length, VA distal part with PICA ostium	PCM, LPT, MPT, MMT, flocculus, cerebellum
5339	Headache				Tetraplegia	Deep coma	BA whole length VA with PICA ostium	PCM, MPT, flocculus, cerebellum

PCM = middle cerebellar peduncle; LPT = lateral pontine territory; LMT = lateral medullary territory; MPT = median pontine territory; MMT = median mesencephalic territory; BA = basilar artery; VA = vertebral artery.

Neuropathological findings

The 7 cases exhibited 23 infarcts of the cerebellum, an average of 3 infarcts per case. There were 6 infarcts in the SCA territory, 8 in AICA territory, and 9 in the PICA territory. Tonsillar herniation was observed in 4 cases. Cerebellar infarcts in AICA territory were associated with infarction in the PICA territory in 3 cases and with infarction in PICA and SCA territories in 4 cases. No association with infarction in SCA territory alone was found. Massive infarction in the paramedian brainstem was noted in 5 cases.

Vascular studies

Five arterial occlusions were observed (3 thromboses superimposed on atheromatous stenosis, 1 postangiographic dissection of the vertebral artery, 1 embolic). Two vertebral artery occlusions were noted, 1 of which was bilateral. Two occlusions of the whole length of the basilar artery were seen, in both cases extending into one of the vertebral arteries as far as the PICA ostium. The last occlusion was in the PICA. In the 2 cases without arterial occlusion seen at postmortem examination, 1 had potentially embolic heart disease (acute myocardial infarction with mural thrombus) and in the other there was postangiographic dissection of the vertebral artery.

Retrospective clinical study

These cerebellar infarcts differed clinically from the preceding cerebellar infarct restricted to AICA territory by the greater frequency of motor weakness and somnolence (either early or delayed), as well as of ocular palsy (especially lateral gaze palsy). Facial and trigeminal nerve involvement could be explained by infarction in the AICA territory and not necessarily by cerebellar swelling with brainstem compression.

Four cases, involving the territories of the 3 cerebellar arteries, presented with deep coma and 2 with tetraplegia. Three cases, involving both the AICA and PICA territories, had a similar clinical pattern to the preceding cerebellar infarcts limited to the territory of the AICA (Table 2). Facial palsy, trigeminal nerve sensory involvement, deafness, a vestibular syndrome and cerebellar dysmetria all occurred. Horner's syndrome and contralateral pain and temperature sensory loss were noted in 1 case. In that case, a common trunk for both the AICA and the PICA arose from the vertebral artery (6523). In another of these cases the same vascular pattern was probable but could not be established (6720). In the last case, the infarct in the PICA territory, on the side opposite to that of the AICA territory, involved only the territory of the lateral branch of PICA (5280), a pattern reported by Adams (1943).

DISCUSSION

Distribution of the infarction

This was usually a pontocerebellar infarction, extending variably through the brainstem and cerebellum. In all cases, the infarction involved the middle cerebellar peduncle, which could be considered as the core of the territory. It frequently extended to the flocculus (69% of cases) (fig. 2C). The involvement of other cerebellar lobules was very common (75% of cases) but usually remained limited. It often affected a small part of the cerebellum comprising the central white matter, the flocculus and a thin rim of cerebellar cortex located at the junction of the territories of the three cerebellar arteries (fig. 2B, D). It could also affect the anterolateral part of the cerebellum in cases with a hypoplastic PICA (the AICA taking over the usual territory of the lateral branch of the PICA). This explains the absence of cerebellar infarction with brainstem compression and tonsillar herniation in these cases with ischaemic lesions restricted to the AICA territory. The vermis was mildly involved only once, in a case with bilateral infarction, confirming that this is not a territory usually supplied by AICA.

The infarction usually extended to the lateral part of the pons in the middle and lower parts of the pons. At this level, its distribution could be described as a triangle with an anterolateral base and an apex directed towards the fourth ventricle, between the middle cerebellar peduncle and the anterolateral pontine region (figs 1, 2B, D, 3B, C). It frequently involved the nuclei and roots of the fifth, seventh and eighth nerves (which characterized the clinical syndrome), the lateral reticular formation, the corticotegmental tract, the lateral lemniscus, the trapezoid body, the anterolateral spinothalamic tract (which explains the crossed sensory syndrome), and rarely the root of the sixth nerve. The abducens nucleus was never involved. The vertical extent of the infarction (fig. 3) was from the junction of the superior and the middle thirds of the pons (i.e. at the level of the root of the fifth nerve) (figs 2A, 3A) to the pontomedullary junction, including the superior part of the lateral medullary region (fig. 3D). This explains the occurrence of difficulty in swallowing and phonation (in half of the cases), which did not appear to be related in every case to a pseudobulbar palsy, but could occasionally be attributed to the involvement of the nucleus or the fibres of the ninth nerve.

The lateral pontine territory has been divided by Duvernoy (1978), from the lower to the upper pons, onto the inferolateral, lateral anterior (lateral midpontine), and posterolateral (lateral superior pontine) regions. In the cases in the present series, the infarction involved the inferolateral pontine region (fig. 3B, C), which is supplied (according to Duvernoy, 1978) by the AICA, and the lateral midpontine region (figs 2A, 3A), which is supplied (according to the same author) by the lateral group of arteries that supply the pons. On the other hand, the lateral superior pontine region, seen only at the level of the superior third of the pons and supplied by the posterolateral pontine arteries and the medial branch of the SCA, was never involved in the infarction.

In Case 6911, a particularly extensive infarct involved the main anterior and lateral part of the inferior cerebellar hemisphere, including the anterolateral part of the tonsil (fig. 2D). A large AICA was occluded. The PICA was macroscopically absent.

Cerebellar infarcts limited to the territory of the AICA were never associated with infarction in the anterolateral or median brainstem on the same side. This contrasted with the cases reported by Brouckaert *et al.* (1981). In the present series, the paramedian brainstem was occasionally involved at the level of the middle and the lower thirds of the pons on the opposite side to the AICA territory infarction.

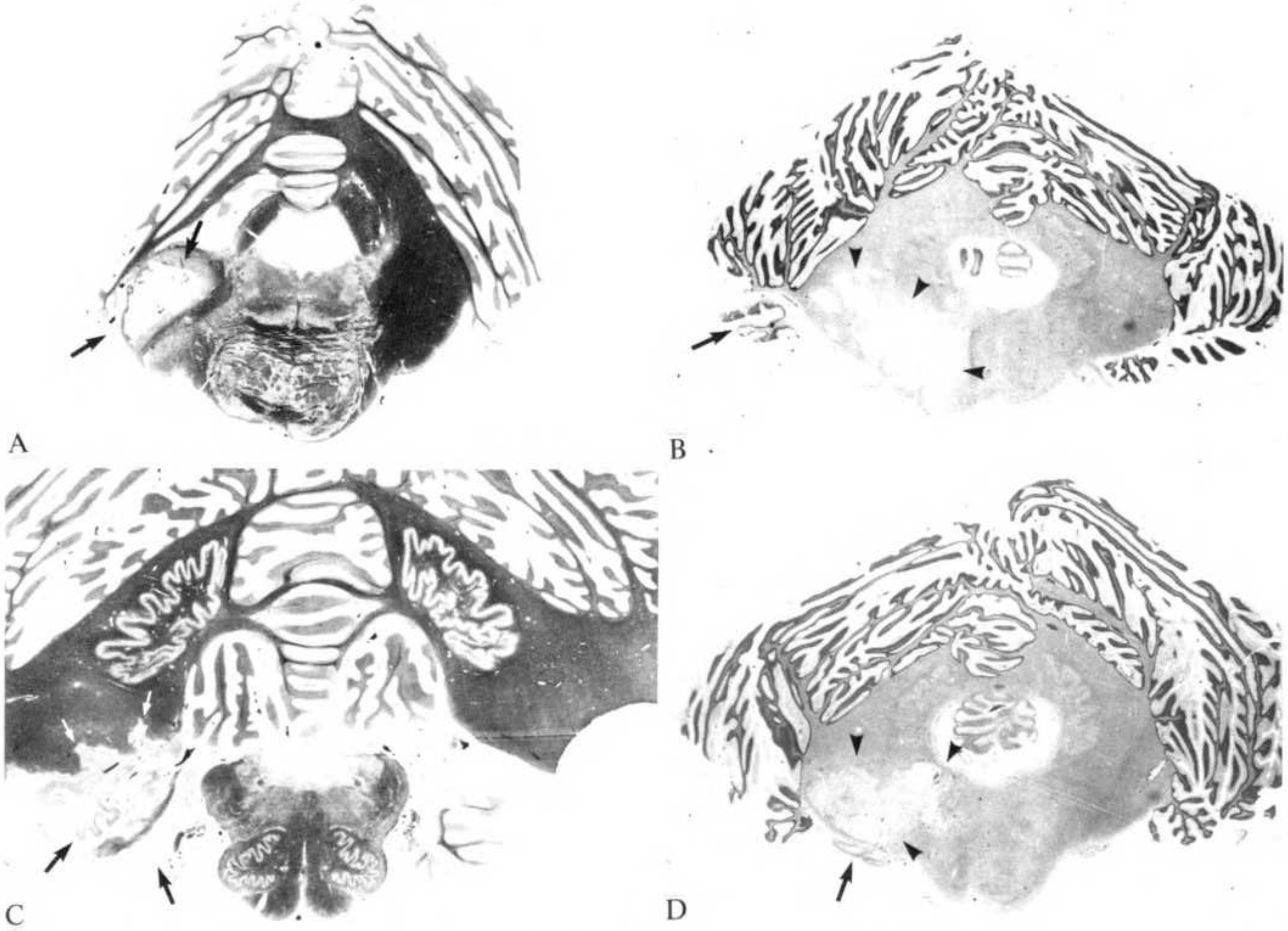

FIG. 2. A, *Case 6056*. Section through the root of the fifth nerve (mid pons). Infarction involving the right lateral midpontine territory and the middle cerebellar peduncle (arrows). B, same case. Section through roots of the seventh and eighth nerves (lower pons) showing infarction extending into the right inferior lateralpontine territory, the middle cerebellar peduncle (arrow heads) and the anterior part of the cerebellum (arrow). C, same case. Section through the mid part of medulla showing infarction involving the right flocculus (arrows). D, *Case 6911*. Section through roots of the seventh and eighth nerves showing infarction involving the right inferior lateral pontine territory, the middle cerebellar peduncle (arrow heads) and the root of the eighth nerve (arrow). A, C, Loyez haematoxylin for myelin (×1.3). B, D, haematoxylin and eosin (×1).

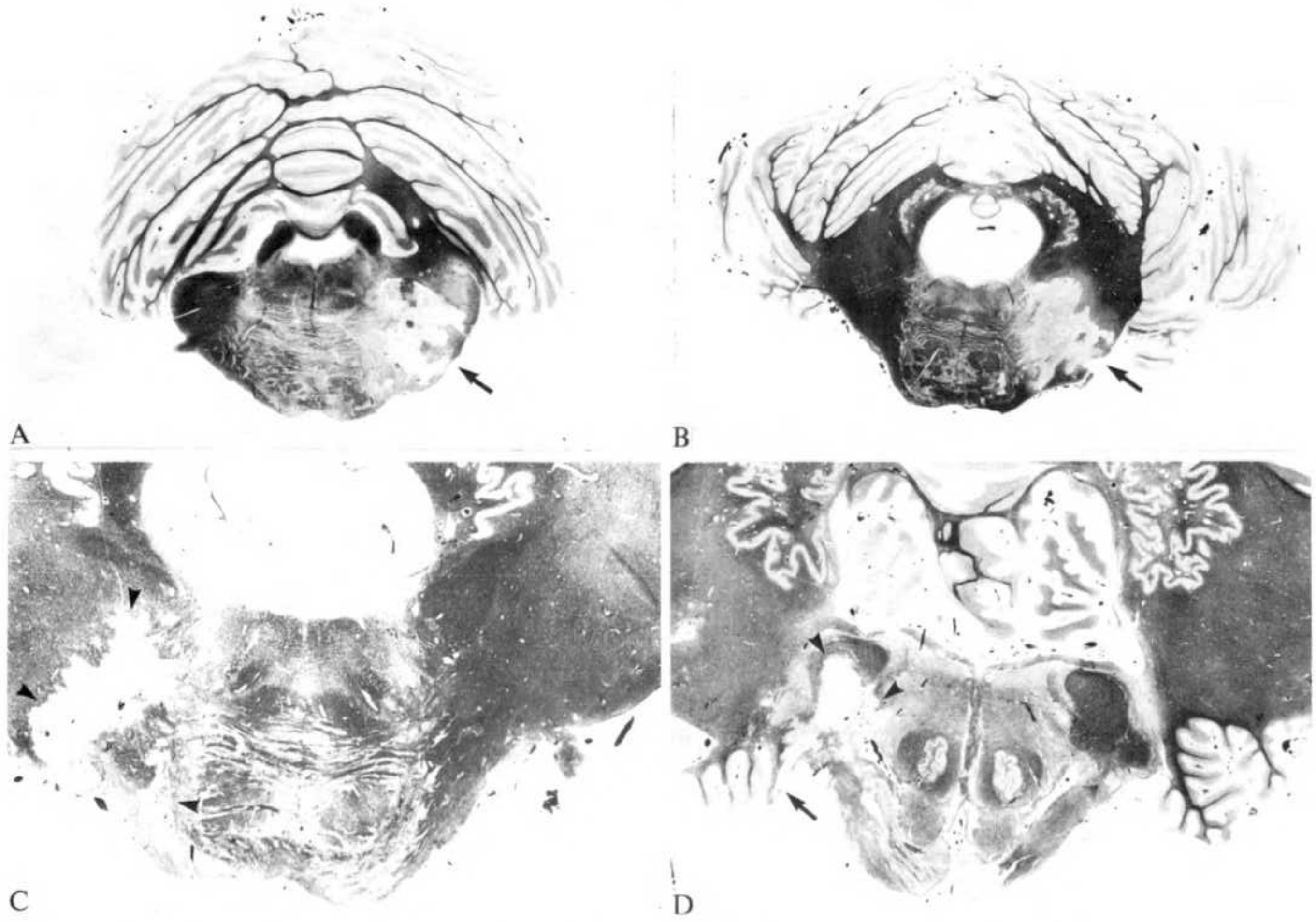

FIG. 3. Rostrocaudal extent of the infarction in the brainstem territory of the AICA. A, *Case 6523*, section through the root of the fifth nerve (mid pons) showing infarction involving the lateral midpontine territory and the middle cerebellar peduncle (arrow) (Loyez haematoxylin, ×1.3); B, *Case 6031*. Section through the nucleus of the sixth nerve showing infarction involving the inferior lateralpontine territory and the middle cerebellar peduncle (arrow) (Loyez haematoxylin, ×1). C, *Case 3175*. Section through the nucleus of the sixth nerve showing infarction involving the inferior lateral pontine region and the middle cerebellar peduncle (arrow heads) (Loyez haematoxylin, ×2.6). D, same case. Section through the upper medulla showing infarction extending down to the upper part of the lateral medullary territory (arrow heads). Arrow points to involvement of the internal part of the flocculus (Loyez haematoxylin, ×2).

Mechanism

The arterial occlusion found at postmortem in most cases could be attributed to thrombosis superimposed on atheromatous stenosis. The occlusion was seldom situated in the AICA, but frequently in the lower part of the basilar artery, and, in a few cases, on the distal part of both vertebral arteries or on the distal part of the ipsilateral vertebral artery. Thus, when the arterial occlusion could be located precisely, it involved mainly the vertebrobasilar trunks, as already noted in other medullary (Fisher *et al.*, 1961; Escourolle *et al.*, 1976) or pontine infarcts (Kubik and Adams, 1946).

Anatomicoclinical correlations

Adams (1943) noted rotational dizziness, vomiting, tinnitus and dysarthria. On the side of the infarction, there were dysmetria, facial palsy, trigeminal sensory impairment, Horner's syndrome and, on the opposite side, pain and temperature sensory loss. In the present series, all these signs were observed with variable frequency. In addition, lateral gaze palsy and dysphagia sometimes occurred. With regard to the very frequently associated motor weakness, it could be explained, in every case, by associated infarcts. A complete clinical syndrome was observed in a few cases (3175, 6911, 6863), among the 13 cases of infarction restricted to the AICA territory. An almost complete syndrome was observed in most cases (5515, 5934, 5060, 6056, 5165, 6031, 6522). A complete syndrome was also noted in some cases of infarction in the brainstem and cerebellar territory of the AICA associated with the involvement of the territory of the PICA (6523, 6720, 5280).

The cerebellar syndrome could be linked to numerous lesions that involved the middle cerebellar peduncle, and/or the restiform body, and/or the ventral spinocerebellar tract or, lastly, the cerebellar hemispheres. The cerebellar signs were never isolated. This contrasts with the case of Marie and Foix (1912) where the only clinical feature was 'hémiplégie cérébelleuse' due to the involvement of a part of the middle cerebellar peduncle at midpontine level (this has been attributed to syphilitic arteritis affecting a few penetrating arteries). The vestibular syndrome was of the peripheral type. According to Lazorthes (1961), the AICA is termed the 'cerebellolabyrinthine artery' because it gives rise to the internal auditory artery in 83% of cases. The labyrinthine type syndrome that follows infarction in the AICA territory could thus be explained by several different lesions: (1) occlusion of the internal auditory artery, accounting also for the tinnitus; (2) involvement of the vestibular nuclei in the pontine tegmentum, or (3) of the fibres of the eighth nerve in the lateral pontine area; or finally (4) involvement of the flocculus or its connections.

Involvement of several cranial nerves in each individual case was constant with the exception of a single case where only the eighth nerve was involved. Paralysis of the fifth and seventh nerves was linked to the involvement of nuclear or intraaxial fibres. Peripheral facial palsy was usually severe. The seventh nerve was the one most frequently involved. In the case of Guillain *et al.* (1929) severe facial palsy, diplopia and mild ipsilateral dysmetria were the only signs of involvement in the territory of AICA. Lateral gaze palsy was more difficult to explain. According to Duvernoy (1978), the AICA supplies the lateral part of the abducens nucleus. However, in the present series, a lesion of the abducens nucleus was never observed. In 1 case, there was involvement of the root of the sixth nerve. The lateral gaze palsy might be explained by involvement of the flocculus rather than the lateral pontine reticular formation (Gilman *et al.*, 1981). Deafness could be linked to the direct involvement of the cochlear nuclei at the pontomedullary junction, or of the lateral lemniscus and the intraaxial fibres of the eighth nerve. Horner's syndrome was explained by the involvement of the pupillodilatator fibres from the hypothalamus in the lateral part of the pons. Pain and temperature sensory impairment was present on the contralateral side of the body without facial sensory loss. It was due to the involvement of the anterolateral (i.e., spinothalamic) tract. Dysphagia was explained in 2 cases by involvement of the superior part of the lateral medullary area (retro-olivary) (fig. 3D). This part of the lateral medullary area is indeed usually supplied by posterior rami arising from the AICA (Duvernoy, 1978).

Motor weakness, observed in nearly half the cases, was linked to associated lesions of the corticospinal tract either at other levels or in the paramedian pontine territory. It must be emphasized that these lesions were *contralateral* to the AICA territory infarction. Motor weakness therefore cannot strictly be included in the AICA syndrome. However, it frequently accompanied the clinical picture of AICA territory infarction.

Thus clinical features of cerebellar infarction in AICA territory mainly depend on brainstem involvement. The contralateral pain and temperature sensory loss, dysphagia, ipsilateral Horner's syndrome, facial sensory involvement, vestibular and cerebellar signs can be mistaken for Wallenberg's syndrome. Moreover, in Wallenberg's syndrome a mild facial palsy has sometimes been reported, and even a lateral gaze palsy with tonic gaze deviation (Kommerell and Hoyt, 1973; Meyer *et al.*, 1980; Cambier *et al.*, 1982). The AICA syndrome, which is normally considered to be rare, is probably hidden behind 'atypical Wallenberg syndromes'. Deafness, tinnitus, massive facial palsy, and multimodal trigeminal sensory involvement could point to a clinical diagnosis of infarction in the AICA territory.

In the case reported by Goodhart and Davison (1936) there was a cerebellar infarct without involvement of the brainstem. The only symptom had been vertigo. Adams (1943) emphasized the fact that the symptoms and signs of the infarction in AICA territory are mainly linked to the brainstem and middle cerebellar peduncle involvement; thus 'when an infarction is limited to the cerebellar hemisphere, vertigo may be the only clinical manifestation, or such a lesion may pass unnoticed and be unexpectedly discovered at autopsy'. Rubenstein *et al.* (1980) reported (Case 1) cerebellar infarct in AICA territory demonstrated by CT and manifested by an isolated labyrinthine type syndrome. This can be compared with cases of infarction in PICA territory also producing an isolated labyrinthine type syndrome (Duncan *et al.*, 1975). This occurs especially when the infarction involves the territory of the medial branch of the PICA (Amarenco *et al.*, 1989).

With respect to the variability of the extrinsic arteries of the brainstem and the fixity of the penetrating arteries (Foix and Hillemand, 1925), the lateral inferior pontine syndrome might also be expected in cases of occlusion of short circumferential arteries supplying the lateral pontine region, usually supplied by small arteries arising from the AICA.

In conclusion, infarction in AICA territory is pontocerebellar in distribution. It involves the lateral pontine region in its middle and lower third and the anterolateral part of the cerebellum, including especially the middle cerebellar peduncle, the flocculus and the anterior part of the cerebellar lobules, with exception of the lobulus anterior.

The clinical manifestation is a crossed syndrome which can be confused with lateral medullary infarction (Wallenberg's syndrome) because of shared signs: dysmetria, vestibular signs, Horner's syndrome, facial sensory impairment and, on the opposite side, pain and temperature sensory loss without facial sensory involvement. Sometimes dysphagia occurs. Taking into account some signs which are unusual in Wallenberg's syndrome, such as severe facial palsy, deafness with or without tinnitus, lateral gaze palsy, multimodal sensory impairment in the face, and skew deviation, it would be possible to predict the precise topography of the infarction.

The frequency of an atheromatous aetiology for the arterial occlusions and of their main location in the distal part of vertebral artery and, more often, in the lower part of basilar artery must be pointed out.

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ABILITY TO DETECT ANGULAR DISPLACEMENTS OF THE FINGERS MADE AT AN IMPERCEPTIBLY SLOW SPEED

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SUMMARY

The ability to detect very slow rotations, which were associated with no sense of movement, was tested at the metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of the middle finger of human subjects. This ability was termed 'position sense'. All the joints were found to have a position sense. No difference in detections of different angular displacements was demonstrated between the joints. Contraction, after the completion of a displacement, of the muscles operating the joints did not alter the position sense. In addition, the DIP joint was also examined in a posture that functionally disengaged its flexor and extensor and no change in position sense was found.

INTRODUCTION

In human subjects, position and movement about a joint can be signalled separately. Distinct awareness of movement and of position have been demonstrated in experiments involving tendon vibration and loading (McCloskey, 1973). Awareness of change of position without the sensation of movement occurs when joints are displaced very slowly (Horch *et al.*, 1975). Clark *et al.* (1985, 1986) showed that the ability to detect a set joint displacement which had been achieved by very slow rotation and had given no sensation of movement, did not depend on the velocity of displacement. They concluded that, as movement signals do depend on velocity, subjects must have a separate static position sense, independent of velocity, that enables them to detect these displacements. They termed this ability 'static-position sense' and defined it as present if there was no decrement in the detection of a chosen amplitude of joint displacement, as the velocity of displacement was decreased. If such a decrement did occur 'static-position sense' was said to be absent (*see* Clark *et al.*, 1985, fig. 1). In addition, they showed that detection of the slowly made displacements was greatly reduced by local nerve blocks said to eliminate muscle afferents while leaving joint and skin afferents intact. Thus it was concluded that '*static*-position sense' depends on muscle receptors.

A sense of joint position, as distinct from movement sense, has been shown at the ankle and at the metacarpophalangeal (MCP) joint (Clark *et al.*, 1985, 1986), at the elbow, through tendon vibration and loading experiments (McCloskey, 1973; Sittig *et al.*,

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1985), and at the knee, by the detection of extremely slow displacements (Horch *et al.*, 1975). However, on testing the proximal interphalangeal joint (PIP), Clark *et al.* (1986) found no separate position sense. In contrast to the MCP joint at which flexion-extension displacements of 2.5° could be detected at velocities as slow as 0.5 deg/min, joint excursions of up to 35° were not detected at the PIP at 4 deg/min. The ability to detect a 5° displacement, present when the displacement velocity was 100 deg/min, diminished with decreasing velocity. Thus there was a sense of movement but *no* 'static-position sense' at the interphalangeal joint, although at the adjacent MCP joint, a 'static-position sense' was present.

Proprioceptive sensation in the fingers is believed to come from a combination of signals from muscle, joint and cutaneous receptors (Cross and McCloskey, 1973; Gandevia and McCloskey, 1976; Gandevia *et al.*, 1983; Clark *et al.*, 1986; Ferrell *et al.*, 1987; Ferrell and Smith, 1987; McCloskey *et al.*, 1987). While muscle and joint receptors contribute quantitative signals, cutaneous input plays a facilitatory role (Gandevia and McCloskey, 1976; Clark *et al.*, 1986). The sense of 'static-position', however, is said to depend solely on signals from muscle receptors (Clark *et al.*, 1985).

The interphalangeal joints of the hand are moved primarily by the long flexors and extensors of the digits. In the relaxed hand, the complex anatomical arrangement of these muscles with their passage over as many as four joints, together with the elasticity of the tendons (Rack and Ross, 1984), make it possible that only a small fraction of the displacement at the distal end of a tendon is conveyed to its muscle. It is conceivable that this diminution of the stimulus to the muscle caused by the mechanical properties of its coupling could explain the failure of Clark *et al.* (1986) to demonstrate 'static-position' sense in the interphalangeal joints of the relaxed hand.

In the present study, we investigated the possibility that cocontraction of flexors and extensors, while not changing the position of the finger, might eliminate slack from the tendons and aid detection of joint displacements by causing greater changes in the length of the muscle fibres. The ability to detect angular displacements made at an imperceptibly slow speed, hereafter referred to as 'position sense', was examined at the joints of the middle finger. The MCP, PIP and DIP (distal interphalangeal) joints of the finger were studied both when their operating muscles were relaxed and when these muscles were actively cocontracting. In addition, because of a tendon arrangement that allows the muscles to be decoupled from the DIP joint by positioning of the hand (Gandevia and McCloskey, 1976), we were able to test the DIP joint in the presence and absence of signals generated by muscle stretch.

METHODS

Position sense in the finger was tested in 5 normal right-handed subjects who were unaware of the hypotheses being tested. They were paid a fee for their participation. The right middle finger was flexed or extended about each joint through various angles at a very slow velocity (2 deg/min). At this velocity, as has been previously described (Clark *et al.*, 1986), subjects could report no movement. Subjects' ability to detect the angular displacements was a measure of position sense at each joint.

The metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints were each examined while the other joints were immobilized. Because of their anatomical arrangement it is possible, by posturing the hand, to slacken the tendons of the muscles operating the DIP joint of the middle finger (Gandevia and McCloskey, 1976) thereby ensuring that imposed movements at the joint do not pull upon their muscles. Thus position sense at the DIP joint was tested twice, both with muscles engaged and with muscles disengaged.

Apparatus

Each joint was tested with the hand and forearm splinted and their ulnar borders resting on a bench top. The arm was screened so that subjects could not see it below the elbow. An electromagnetic vibrator (Advanced Dynamics Industries AV-50) driven by a ramp function was used to move the finger about each joint in a series of discrete steps, the amplitude of each of which was less than 0.08°. The vibrator was linked to the finger by a metal rod which pivoted on pin joints at each end. Each joint was initially positioned in the centre of its range of movement and displacements were confined to a range where external clues to change of position, such as bulging or stretching of skin around the joint, were minimal (that is, were denied by subjects). All splints and fixation devices were firmly applied so that any changes in pressure were a small proportion of total pressure. The finger was left free as far proximal and distal as possible to the joint being moved to minimize any impingement of the skin on the fixation devices.

For the MCP joint, the hand was secured by a 'Y'-shaped splint on its volar surface. The index finger was strapped to one of the limbs of the 'Y' while the ring and little fingers were fastened to the other. The middle finger projected between the limbs of the 'Y' and could move freely at the MCP joint. The PIP and DIP joints were held extended by an individually moulded thermoplastic splint and carrier to which the vibrator was attached. The splint was a stiff sheath surrounding the finger from the fingertip to just proximal to the PIP joint. The finger was initially held at approximately 5° – 10° flexion and was displaced by 1.25°, 2.5°, 5° and 10°.

To test position sense at the PIP joint, the middle finger was immobilized and supported by a clamp holding the proximal phalanx and was fitted with a moulded carrier splinting the DIP joint in extension. The distal half of the proximal phalanx, PIP joint and proximal half of the middle phalanx were kept free. The fourth and fifth fingers were held extended and the index finger was bent to 90° at the PIP joint. The middle finger was flexed or extended about the PIP joint, from a starting position of 30° –40° flexion, through angles of 2.5°, 5°, 10° and 20°.

The DIP joint, in the 'muscles engaged' position, was examined with all the fingers held in extension by a splint on the palmar surface of the hand. The distal half of the middle finger protruded beyond the splint and allowed free movement at the DIP joint. A bar clamped across the proximal part of the middle phalanx secured the finger and ensured that the PIP joint remained in extension. In the 'muscles disengaged' posture, the hand was held by a device previously described by Gandevia and McCloskey (1976). The middle finger was fully flexed at the PIP joint while the other fingers were held extended at MCP, PIP and DIP joints. No voluntary movement above the DIP joint was possible but passive movement was free. In both postures, the distal phalanx was displaced 2.5°, 5°, 10° and 15° from an initial position of approximately 20° flexed.

At each of the joints, displacements were calibrated by fastening a long thin pointer to the finger and measuring the angle through which it passed. The calibration pointer was removed before trials commenced.

Paradigm

For each joint (MCP, PIP, DIP—muscles engaged, DIP—muscles disengaged), each subject completed 50 trials over two sessions of about 3 h each. The 50 trials included 5 flexions and 5 extensions at each of 4 angular displacements and 10 trials of zero displacement. When the finger remained stationary the durations of the trials were varied to correspond to the durations of trials at other displacements. Trials were presented in pseudorandom order of magnitude and direction of displacement.

Each trial consisted of a very slow movement from the starting position with the hand held relaxed, and an identification (*see* below), at the conclusion of displacement, of the direction of the new position relative to the starting position. This was followed by active tensing of the finger (except for the DIP joint in the 'muscles disengaged' posture) by cocontraction of the flexor and extensor. A repeat identification of the direction of the new position relative to the starting position was made. The finger was then returned to the starting position at a rapid, perceptible velocity. During the slow displacement, subjects were instructed to try to ignore the finger and were encouraged to read or otherwise distract themselves.

In identifying the direction of displacement subjects were allowed to answer 'bent' (for flexion), 'straightened' (for extension) or 'I don't know'. They were allowed to take as long as necessary to decide on an answer and some subjects took up to 2 min. Subjects were encouraged to be *sure* before identifying any perceived change of position. A pay-off scheme gave them a bonus 50 cents over the agreed fee for correct answers but docked $1 for wrong answers, while 'I don't know' was not penalized. Any subject with more than 20% (10 of 50) false responses (wrong direction, or a displacement nominated when none had occurred) for any joint, was discarded from the experiment. In practice, subjects who performed satisfactorily for one joint performed satisfactorily for all joints tested. In a preliminary experiment examining only the PIP joint, 4 out of 11 subjects were discarded. In this study, 1 of 8 subjects was discarded, although 2 other subjects dropped out because of other commitments. However, 4 'retainable' subjects in the main study had completed the preliminary experiment successfully (and with similar results).

Data analysis

Working with the figure of 20% false positives (the maximum permitted) and assuming these were all wrong guesses, we can also assume that a like number of correct guesses were made. Thus up to 20% of answers would be guessed correctly. This means that if the displacement of the joint could not be detected, subjects' means score could be expected to be 2 of 10 trials *correct* (guessed) 2 trials *incorrect* (guessed) and 6 trials answered 'I don't know' (*not guessed*). For each angular displacement, for each joint, the correct identification of the direction of 2 of the 10 trials would be a chance score. Correct identification of more than 2 trials is a score above chance ($P < 0.5$) and the probability of correctly identifying more than *4* (from 5 flexions and 5 extensions) would be greater than chance at a significance level of $P < 0.05$.

RESULTS

Position sense of the joints of the right middle finger was measured by subjects' abilities to report the direction of displacements of various magnitudes about each joint. At each of the joints tested (MCP, PIP, DIP—with and without muscles engaged) all subjects were able to detect displacements provided the displacements were large enough.

Fig. 1 shows each subject's detection scores on an individual graph. The scores for each joint at all angular displacements tested are shown. Any symbol marked on or above the dotted line represents a significantly greater-than-chance detection of displacement. Although there is considerable variation between subjects and between joints for some subjects, most subjects detected displacements of 10° at most joints and more than half at displacements of 5°.

To enable comparison between position sense at each joint a 'threshold' for detection of displacement was chosen. The smallest magnitude of displacement, at which a line, joining points on the number of detections versus displacement plot, reached 5 correct detections was decided on as the 'threshold'. Five is the smallest number of correct detections to be *significantly* above chance ($P = 0.03$; 4 is above chance at a level of $P = 0.12$). Fig. 2 (opens symbols) shows these thresholds for the relaxed finger. Overall, subjects were not better at detecting displacements at one joint than another. An analysis

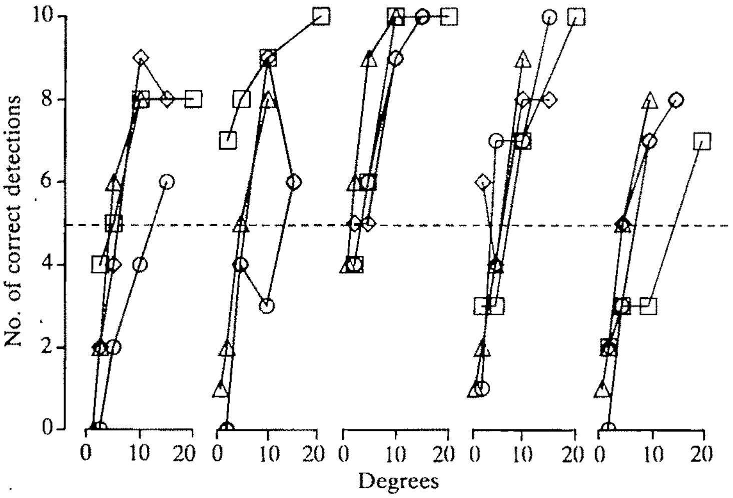

FIG. 1. Data from 5 subjects are plotted on separate graphs. The number of correct detections of direction of joint displacement in the relaxed finger is plotted for 4 magnitudes of displacement at the MCP (triangle), PIP (square) and DIP joints of each subject. The DIP joint was tested with (diamonds) and without (circles) its operating muscles functionally engaged.

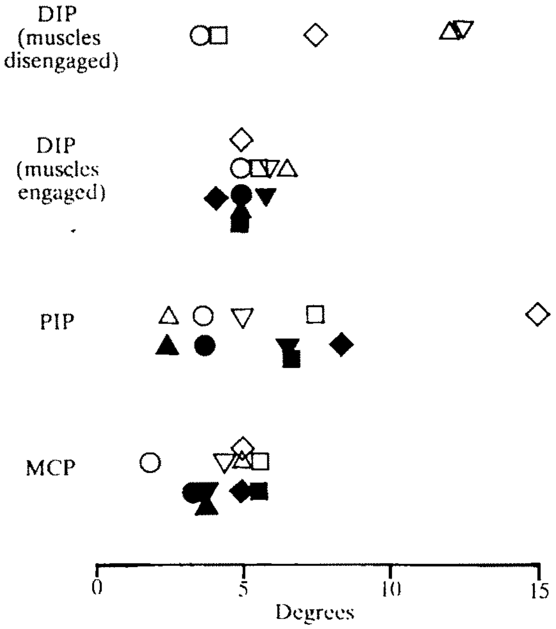

FIG. 2. 'Threshold' displacements (*see* Results) for the detection of direction of joint displacement are shown for the MCP, PIP and DIP (with and without muscles engaged) for each of 5 subjects. Open symbols are 'thresholds' for the relaxed finger. Closed symbols show 'threshold' for joints in the finger with cocontracting flexor and extensor.

of variance (ANOVA) showed no significant differences between detection 'thresholds' of the joints. Equally, there was no difference between the MCP, PIP and DIP joints when the muscles were tensed (fig. 2, closed symbols).

Contraction of the flexors and extensors of the finger after the finger had reached its new position made no difference to the abilities of subjects to detect the direction of displacements. Fig. 3 compares the number of detections at each angular displacement for each joint when the finger was relaxed and when it was tensed. Each joint of each subject is plotted separately. A paired t test comparing detection 'thresholds' at the relaxed joint with those after cocontraction did not show a significant difference ($P > 0.2$).

The DIP joint was studied under three conditions, with muscles relaxed, with muscles

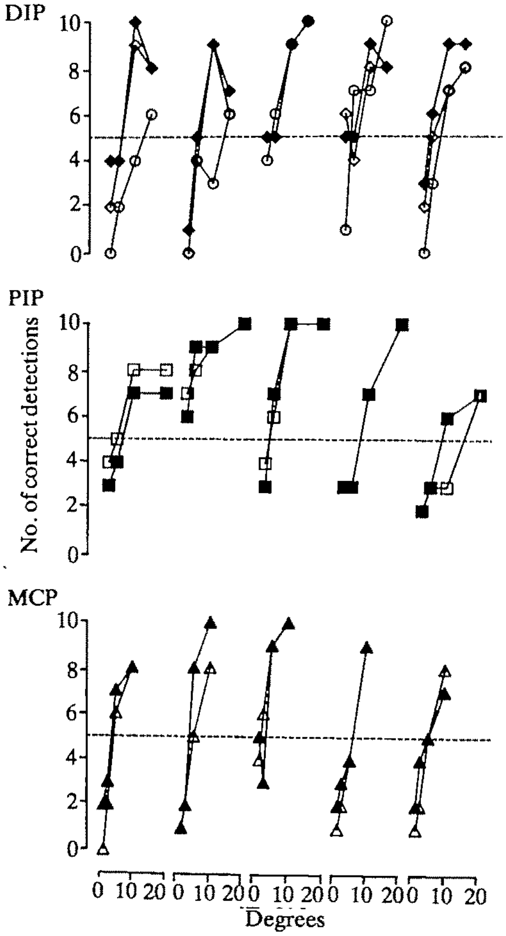

FIG. 3. Correct detections of 4 magnitudes of joint displacement at each of 3 joints are compared with relaxed and with tensed flexor and extensor pairs. Open symbols represent the joints with relaxed muscles; closed symbols, with tensed muscles. Where closed symbols appear alone, detection scores for relaxed and for tensed muscles are identical. The *top panel* shows results for the DIP joint under 3 functional conditions: muscles disengaged (circles); muscles engaged but relaxed (open diamonds); and muscles tensed (filled diamonds). The *middle panel* and *bottom panel* show data for the PIP and MCP joints, respectively. The 3 joints of an individual subject are shown in a vertical line.

cocontracted and with muscles decoupled from the joint. In comparing the 'thresholds' in fig. 2, more intersubject variation is apparent when the muscles were disengaged than under the other two conditions. However, statistical comparison (two-way ANOVA) showed no significant differences between 'thresholds' at the DIP joint with or without muscle involvement.

DISCUSSION

The present study has demonstrated position sense in the metacarpophalangeal and both interphalangeal joints of the middle finger of normal subjects. No improvement in performance was demonstrable when muscles that operate the joint were contracted without moving the joint. The threshold for detectable displacements, made at imperceptibly slow speeds, was similar at all joints. No difference in position sense was demonstrated at the distal interphalangeal joint when the hand was postured so as functionally to disengage the muscles at that joint.

Our findings differ from those of Clark *et al.* (1986). These workers reported absence of 'static-position sense' (inability to detect very slow displacements of as much as 35°) in the interphalangeal joints, in contrast to good 'static-position sense' (reliable detection of 2.5° displacement) at the metacarpophalangeal joint. We cannot satisfactorily explain the differences in results. It cannot be, as we originally thought, that slackness and distensibility of the long digital tendons had prevented joint movements from pulling on remote muscle bellies, because we found here that cocontraction of the flexor-extensor pairs at the interphalangeal joints did not improve detection performance.

Possibly our testing procedures encouraged subjects to reach consistent decisions on the basis of slight and unobtrusive signals, whereas those of Clark *et al.* did not. We used a financial reward/penalty system to encourage motivation and concentration, but excluded subjects who made more than 20% incorrect decisions. Clark *et al.* discouraged guessing, and recorded 'false alarms' and 'false responses' in fewer than 2% of trials. Another difference was that we allowed choices of 'bent', 'straightened', or '*don't know*' in contrast to 'higher', 'lower' and '*no change*' in the study of Clark *et al.* (1986). If 'no change' was the only available response for both 'don't know' and 'not sure' and, moreover, 'not sure' was a condition subjects and experimenters preferred to a false alarm or false detection, then Clark *et al.* may have inadvertently invited their subjects to indicate no change when, in reality, they perceived *something* but were less sure about it than they might have liked. Thus the apparent contradiction between our findings at the interphalangeal joints and those of Clark *et al.* (the presence compared with the absence of a position sense) may be less due to a complete disparity in results than to a difference in degree arising from criterion levels and also a difference in interpretation.

Some of the difficulty in reconciling the findings may come from the definition of 'static-position sense'. 'Static-position sense' is defined by Clark and his colleagues as absent if there is a decrement, with decreasing velocity of displacement, in the ability to detect a joint displacement of chosen amplitude. Thus if there is no decrement 'static-position sense' is present. This definition assumes that position sense and movement sense are equally sensitive to a displacement of the chosen amplitude. However, if the ability to detect displacements varies with amplitude, as well as with velocity, the choice of amplitude of excursion might be critical. At a given amplitude of displacement, position sense may be less effective than movement sense at detecting the excursion. Decreasing the velocity of displacement would then continue to cause a decrement in detection until the slowness of the displacement caused the efficacy of detection by movement sense to drop to match the ability to detect displacements using position sense. Detection should then drop no further.

We believe that this decrement in detection ability would not indicate the absence of position sense but would confirm the presence of a movement sense and would indicate that position sense was not as sensitive as movement sense in detecting the set displacement. The absence of position sense at a joint could only be confirmed by displacing the joint through its full range and finding that detection was at chance level. Our results, which indicated that detection of displacements did vary with amplitude of displacement, did not confirm the absence of position sense at the interphalangeal joints. Displacements in this study were made at the slowest velocity used by Clark *et al.* (1986) in testing the PIP joint and subjects had no sense of movement. Thus there is a sense of position at the interphalangeal joints although there may be no 'static-position sense'. However, different definitions of position sense and different criterion levels in the studies cannot explain the difference between the PIP and MCP joints found by Clark *et al.* but not confirmed in the present study. We found no difference between position sense in the MCP joint and that in the interphalangeal joints. Despite our subjects' lower criterion levels 'threshold' displacements at the MCP joint were larger than or equivalent to the 2.5° displacements that could be reliably detected in the work of Clark *et al.*.

The present findings suggest that proprioceptive sensation in the fingers is less complicated than the results of Clark *et al.* imply. Clark *et al.* were compelled to postulate that the interphalangeal joints of the fingers are quite unlike all other joints because they cannot give rise to a static-position sense. They did so, drawing attention at the same time to the limited ability one has to position the two IP joints of a finger independently of each other, and noted that 'if this limited ability . . . results from mechanical limitations of the muscles and joints . . . rather than from a limited ability of the motor system to set the lengths of individual muscles, it might be anticipated that muscle receptors alone could not encode certain possible positions of the IP joints. Therefore, a static-position sense, if one does exist with these joints, would differ from that with other joints'.

This argument, however, is based on the assumption that position sense is based solely or predominantly on the discharges of intramuscular receptors. In favour of that conclusion is the earlier study by Clark *et al.* (1985) in which position sense was greatly blunted by procedures intended to eliminate inputs from intramuscular receptors. Thus, for example, local anaesthetic block of the common peroneal nerve at the knee paralysed the ankle dorsiflexors and markedly decreased detection of slow displacements when the plantar flexors (unaffected by block) were slackened but not when the plantar flexors were stretched. In addition, block of the ulnar nerve at the wrist which paralysed the interosseous muscles that abduct and adduct the MCP, but 'presumably left skin and joint receptors unaffected', was also associated with marked reduction in detection performance for 'static-position sense'. However, it should be noted that it was a presumption rather than a demonstration of no effect on skin and joint receptors upon which the deduction was made. Further, although performance at the MCP joint was greatly impaired ~20% detection still occurred. This level was still above chance as false positives were restricted to 2%. Thus some position sense remained without muscle receptor input.

The present study does not support the proposal that muscle receptors are solely responsible for normal position sense. Tensing the muscles about an immobile joint was not demonstrated here to improve detections of static position. Furthermore, functional disengagement of the muscles at the DIP led to no demonstrable reduction in detection performance. These observations do not indicate, of course, that muscle receptors cannot or do not subserve position sense, but only that if they do so, in the fingers, their normal contribution is duplicated by contributions from other sensory receptors, such as joint or cutaneous receptors. Clark *et al.* (1986), for example, showed that removal of inputs from joint receptors by intracapsular injection of local anaesthetic does not impair movement sense at an interphalangeal joint when muscle afferents are available to compensate for the loss, although Ferrell *et al.* (1987) showed that similar articular anaesthesia does diminish this sense when muscle afferents cannot compensate. Clearly, there is a degree of overlap and potential mutual compensation between muscle and joint receptors. The recent demonstration by Burke *et al.* (1988) that a small proportion of receptors from human digital interphalangeal joints have modulated discharge across the full range of joint excursion removes any basis for believing that joint receptors could not underlie static position sense in the digits because they discharge only at extremes of joint excursion (*see*, e.g., McCloskey, 1978, for review). Certainly, if position sense is subserved both by muscle and joint receptors the contribution from each may vary for different amplitudes of displacement and for different joints. Input from muscle receptors may well be less important in the fingers than at larger joints for the angular displacements used in this study. For movements of the distal interphalangeal joint, made at faster velocities, the threshold amplitude for detection is more than ten times that of the elbow and shoulder when the thresholds are expressed as angles of joint rotation (Hall and McCloskey, 1983). However, when expressed as proportional change in muscle length the thresholds were similar. Thresholds for the detection of movements of different velocities at ankle are similar to those of the shoulder and elbow (Clark *et al.*, 1985) and the threshold for detection of static displacement at the ankle is ~3°. If the relationship between proportional change in muscle length and threshold displacements remains true at very slow velocities a displacement of ~30° of the DIP joint might have an effect on muscle receptors comparable with the 3° threshold ankle displacement. For smaller displacements of the distal interphalangeal and other finger joints, the contribution of muscle receptors to position sense is likely to be less than it is for larger, more proximal joints displaced through the same angles.

Finally, the possibility must be considered that in the present study, but not in that of Clark *et al.* (1986) which found no digital position sense, detections of altered static position at the interphalangeal joints were based not upon specific proprioceptive inputs, but upon accessory clues of various kinds. Bulging of the skin at or near the displaced joint is probably the most likely source of such accessory clues, and we attempted to minimize it. Also, subjects denied feeling any changes in the skin. Nevertheless, this or other accessory clues at the interphalangeal joints cannot be entirely excluded. They would, however, have to be sufficiently consistent to account for position sense of similar threshold and range to that at the MCP.

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BARORECEPTOR DYSFUNCTION IN ACRYLAMIDE AXONAL NEUROPATHY

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SUMMARY

Clinical studies suggest that baroreceptor dysfunction may occur in peripheral neuropathies but this abnormality has never been observed directly or characterized. Carotid sinus nerve and depressor nerve activity was recorded in rabbits with a mild axonal neuropathy produced by acrylamide. Arterial pressure was changed by altering intravascular volume. The pattern of baroreceptor discharge in the affected animals was always different, there being a marked reduction of diastolic phase nerve activity at normal arterial pressures. In addition, nerve activity in both baroreceptor nerves was significantly reduced. The thresholds of aortic arch baroreceptors were elevated and aortic arch baroreceptor activity was less than carotid sinus baroreceptor activity at lower arterial pressures. In acrylamide axonal neuropathy, even when mild, there is baroreceptor dysfunction.

INTRODUCTION

Baroreceptors have not been assigned a primary role in any human disease process, despite extensive studies. Although clinical investigation of patients with peripheral neuropathies has suggested that some baroreceptor reflex dysfunction occurs commonly (McLeod and Tuck, 1987; Ewing, 1988), there is little evidence for abnormalities of the baroreceptors themselves. Recent autopsy evidence suggests that the carotid sinus nerve can be damaged in patients with diabetes and chronic alcoholism (Tamura *et al.*, 1989) and there is indirect evidence for acute baroreceptor dysfunction in the Guillain-Barré syndrome (Fagius and Wallin, 1983). The likely mechanism of this latter baroreceptor dysfunction is acute demyelination of both vagus and glossopharyngeal nerves, the baroreceptor itself not being involved. There has been no direct evidence of dysfunction of the baroreceptors or their innervating nerve fibres either in human or animal neuropathies.

It is likely that baroreceptor abnormalities in axonal neuropathies will not be uniform. In animals with acrylamide axonopathy, baroreceptors innervated by vagal nerve fibres reflexly affect heart rate, arterial pressure and renal sympathetic nerve activity less than carotid sinus baroreceptors (Satchell, 1984, 1988, 1989). The most vulnerable group of arterial baroreceptors whose afferent fibres travel in the vagus should be the aortic arch receptors innervated by myelinated fibres, because unmyelinated nerve fibres and their receptors tend to be spared in distal axonopathy produced by acrylamide (Spencer

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and Schaumburg, 1974). This most vulnerable group of arterial baroreceptors should have the lowest pressure thresholds, and the highest sensitivities (Thoren and Jones, 1977; Brown *et al.*, 1978; Coleridge *et al.*, 1987).

The proposition examined in the present study is that baroreceptor dysfunction exists in acrylamide neuropathy and it should be more evident in the baroreceptors of the aortic arch rather than those of the carotid sinus. A preliminary description of the alterations in baroreceptor discharge patterns in acrylamide neuropathy has been published (Satchell, 1988).

METHODS

Five NZW rabbits (2.0–3.7 kg, both sexes) were given acrylamide subcutaneously twice a week for 8 to 10 doses at a dose level which ensured that the final amount of acrylamide given was between 300 and 400 mg·kg^{-1}. This group of animals and the control group of 5 animals received vegetable supplementation to their normal rabbit food. No more than 2 animals from either group were studied in successive experiments.

The neuropathy that this dose regimen induced was very mild. The principal clinical sign, if any was present, was that the carriage of the hindquarters was lower than normal. Minimal ataxia was sometimes observed on a carpet. Foot folding and subtle changes in hopping gait were less reliable signs. The clinical signs and dose of acrylamide are given in Table 1. Motor nerve conduction abnormalities exist in animals which have received similar doses of acrylamide (Satchell, 1985).

TABLE 1. CLINICAL FEATURES

Animal	*Low hindquarter carriage*	*Ataxia*	*Acrylamide dosage (mg·kg^{-1})*
A1	–	–	300
A2	+	+	353
A3	–	–	343
A4	+	+	397
A5	+	+	359

Anaesthesia

Induction was achieved with intravenous pentobarbitone (30 mg·kg^{-1}) given via an ear vein. Further anaesthetic doses were given during surgery as boluses via a femoral vein catheter. A 5% dextrose solution was infused throughout the experiment, starting at 2 ml·kg^{-1}·h^{-1} (McGaw Volumetric Infusion Pump). During recordings, anaesthetic was given either via the infusion or as frequent small boluses. A tracheostomy piece was inserted low in the trachea. The animals breathed spontaneously, anaesthetic administration being regulated to keep the end expired percentage of carbon dioxide between 4 and 5%. Catheters were inserted into the right carotid and femoral arteries. Subcutaneous local anaesthetic (xylocaine 1%) was used before all skin incisions. Rectal temperature was maintained between 38.5 and 39.5° C. Arterial oxygen and carbon dioxide tensions were determined throughout the experiments with a blood gas analyser (ABL2 or a Nova Stat Profile 4). Sodium bicarbonate was given as required.

Nerve recordings

The cervical oesophagus and trachea and the caudal pharynx and larynx were removed. The left carotid sinus nerve was identified from its junction with the glossopharyngeal nerve and cut. It and the cut aortic depressor nerve were placed on platinum hook electrodes. All the phasic components of the carotid sinus nerve discharge were removed when the common carotid artery was occluded just caudal to the carotid bifurcation. The nerve sheaths were not removed and the band width of the multifibre recordings was 5–3000 Hz. The nerves were covered in warmed paraffin. A catheter in the right carotid artery was advanced to the level of the aorta. Different levels of arterial pressure were obtained by first withdrawing 15–25 ml of blood from the femoral arterial catheter, and then slowly reinfusing it. Aortic arch pressure, carotid sinus nerve and aortic depressor nerve activity and the electrocardiogram were recorded on magnetic tape (Racal Store 14DS).

Analysis

In some previous studies in which multifibre baroreceptor recordings have been compared, impulse frequency has been obtained using a window (window height 5 μV; Irisawa and Ninomiya, 1967). In order to remove the bias of losing the smallest impulses window techniques were not used in the present study. Nerve activity was quantified by measuring neurogram area (Aars, 1968). Neurograms were produced from the raw nerve activity, which was filtered (high pass, 200 Hz), full wave rectified and leaky integrated (time constant 10 ms).

The neurograms corresponding to 20 arterial pulse waves were averaged. The area under the averaged neurogram gave a measure, after division by the gain of the recording system, of the amount of nerve activity at a particular arterial pressure. Minimum signal levels were determined from the periods of nerve silence (Aars, 1968). In 1 control animal (C3) and 1 animal affected by acrylamide (A3), technical difficulties resulted in persistent tonic carotid sinus nerve discharge. While the process of leaky integration precluded any determination of the absolute level of nerve activity, the simultaneous production of averaged neurograms by two matched analytic systems allowed comparisons of the amplitude of nerve activities, both within animals and between animals.

Neurogram amplitude was influenced by the degree of electrode nerve contact. This variable could be removed by assigning a value of 100% to the area of the averaged neurogram obtained at an arterial pressure of 100 mmHg, the upper plateau of arterial pressure in conscious rabbits (Dorward *et al.*, 1985). Averaged neurogram areas at other arterial pressures were scaled accordingly. A correction for variations in the length of the cardiac cycle did not alter the differences described in the Results (Aars, 1968). Averaging and manipulation of the neurograms was carried out off-line using the language ASYST (AT microcomputer).

RESULTS

Patterns of baroreceptor discharge in acrylamide neuropathy

In the arterial pressure range of 60 to 100 mmHg, there are two distinct phases of carotid sinus and depressor nerve activity during each cardiac cycle in the rabbit (Aars, 1968). The second phase is related to the pressure changes which occur after aortic valve closure (fig. 1). In all acrylamide animals, diastolic phase activity was reduced in the carotid sinus nerve and virtually absent in the depressor nerve (fig. 1).

The difference in the discharge pattern in affected and control animals became very apparent when the averaged neurograms were compared over a range of arterial pressures (fig. 2). In contrast with control recordings, the baroreceptor discharge in affected animals was dominated by systole-related activity, there often being little other nerve activity in the normal arterial pressure range. At a pressure of 80 mmHg, the normal resting

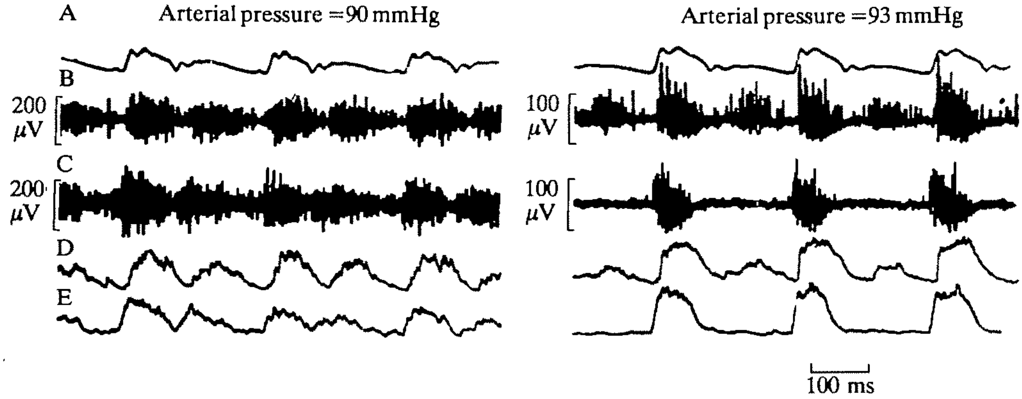

FIG. 1. Comparison of baroreceptor nerve activities in a control rabbit (*left*) and a rabbit with acrylamide neuropathy (*right*). A, arterial blood pressure; B, carotid sinus nerve activity; C, depressor nerve activity; D, carotid sinus nerve neurogram; E, depressor nerve neurogram. There was very little diastolic phase nerve activity in the depressor nerve.

arterial pressure of the rabbit (Dorward *et al.*, 1985), diastolic phase depressor nerve activity was rarely observed. In contrast, control baroreceptor nerves fired relatively continuously through systole and diastole, brief reductions occurring just before the start of diastole and systole at normal arterial pressures (Aars, 1968).

Baroreceptor thresholds

Baroreceptor threshold was determined from the examination of successive averaged neurograms (10 arterial pulse waves averaged); a direct oscilloscope display was used for this measurement in 2 of the animals (C3, A3). Thresholds for both the disappearance of nerve activity during decreases in arterial pressure and for the appearance of activity during increases in arterial pressure were obtained both for the systolic and diastolic phases of the cardiac cycle. All threshold values were averaged for each phase (Table 2).

In both groups of animals the thresholds determined during the systolic phase were lower than the corresponding thresholds determined during the diastolic phase, as observed by others (Aars, 1968). This difference in thresholds occurs because of the different rates of change of arterial pressure during the two phases of the cardiac cycle. The control threshold values for the two phases of the cardiac cycle were identical to those observed previously (Aars, 1968). In the 5 affected animals the diastolic phase thresholds both for the depressor and carotid sinus nerves were all higher than in the control animals. Systolic phase measurements overlapped. The failure to lower the systemic arterial pressure far enough in 2 of the control animals might have contributed to the depressor nerve thresholds not being significantly different during the systolic phase (Mann-Whitney, $P > 0.05$).

Pressure nerve activity relationship

The amplitude of the nerve activities was not determined absolutely but could be compared within each animal and between animals (*see* Methods). There was overlap

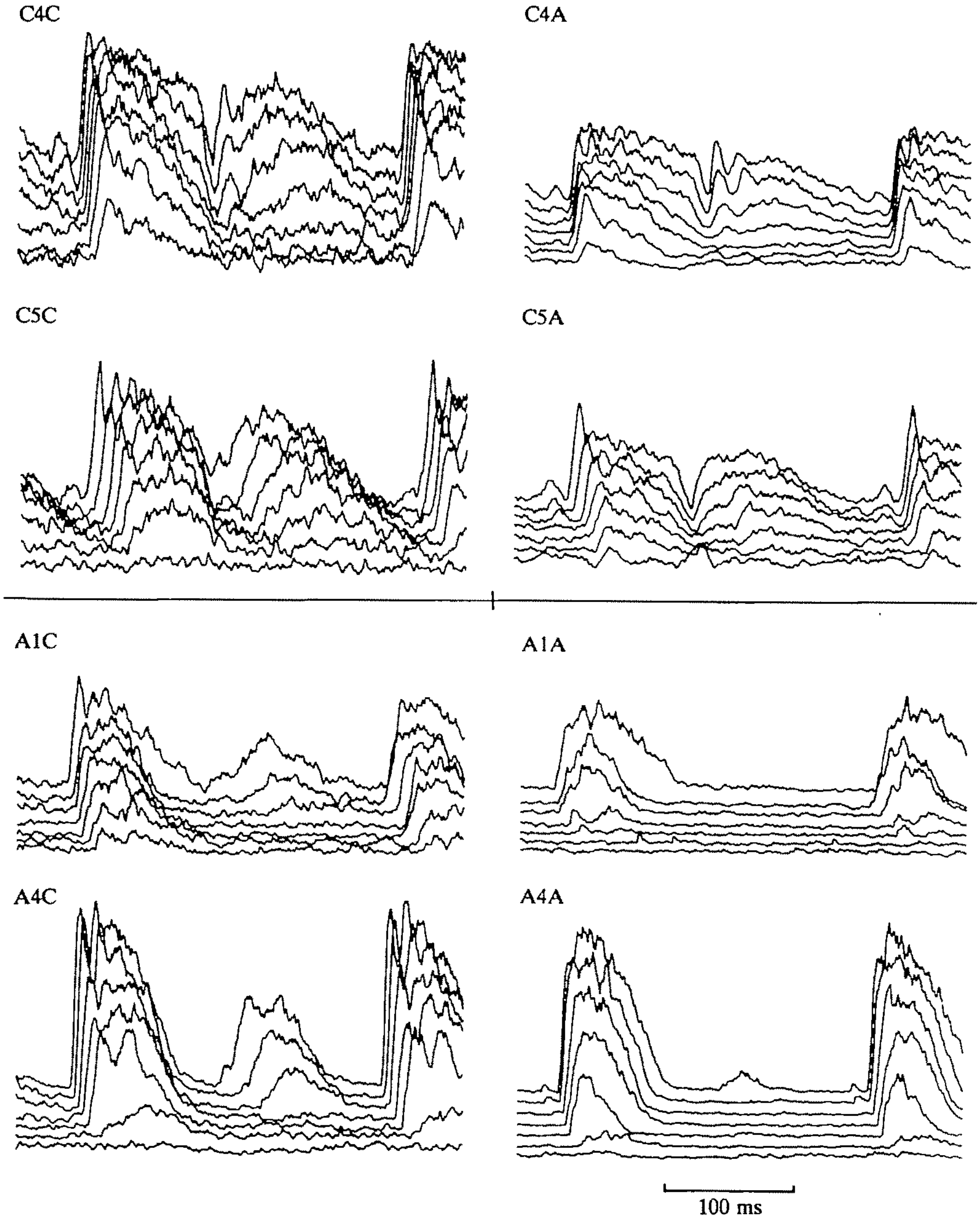

FIG. 2. A comparison of the averaged baroreceptor neurograms in 2 control (*upper half*) and 2 animals treated with acrylamide (*lower half*). Carotid sinus neurograms are on the left and depressor nerve neurograms are on the right. Six averaged neurograms from each nerve are displayed, each trace being the average of 20 cardiac cycles at mean arterial pressures of 40, 50, 60, 70, 80, 90 and 100 mmHg. The averaged neurograms for the depressor nerve (A1A, A4A) have lost virtually all their diastolic phase activity as compared with the control examples (C4A, C5A). There is also some reduction in the relative amount of carotid sinus nerve activity in the affected animals (A1C, A4C). These averaged neurograms have not been normalized. (Gains: C4C,C4A = ×10,000; C5C,C5A = ×10,000; A1C,A1A = ×12,500; A4C = ×5000, A4A = ×10,000.)

TABLE 2. BARORECEPTOR THRESHOLDS

	Carotid sinus nerve		*Aortic depressor nerve*	
	Systolic phase (mmHg)	*Diastolic phase (mmHg)*	*Systolic phase (mmHg)*	*Diastolic phase (mmHg)*
Controls				
C1	<54	<54	<54	<54
C2	35	64	32	64
C3	46	67	46	67
C4	<36	56	<36	67
C5	40	55	40	63
Acrylamide				
A1	49	81	54	99
A2	<40	69	48	72
A3	48	77	51	77
A4	43	70	47	96
A5	56	75	56	81

of the carotid sinus nerve activity amplitudes in the two groups of animals over the arterial pressure range of 40–100 mmHg. In contrast, there was no overlap in the amplitudes of the depressor nerve recordings up to an arterial pressure of 80 mmHg (fig. 3). Nerve recording amplitudes are affected by nerve electrode contact. When normalized nerve activities were compared, both the carotid sinus and the depressor nerves were impaired for arterial pressures up to 80 mmHg in the affected animals (fig. 3).

The differences in normalized carotid sinus and depressor nerve activity within each animal appeared more pronounced in the affected animals (fig. 4). A comparison of these differences between the two groups of animals showed that they were much larger in the animals with neuropathy (Mann-Whitney, $P < 0.001$; $Z = 3.599$, 40 deg of freedom), implying that the depressor nerve of the affected animals was relatively more damaged.

DISCUSSION

In the present study, direct recordings of carotid sinus and depressor nerve activity in rabbits with mild acrylamide neuropathy demonstrated that there was baroreceptor dysfunction. It is likely that abnormalities of the baroreceptor and its innervating nerve fibre are partly responsible for the alteration in baroreceptor reflex function frequently observed in clinical autonomic studies in the common sensorimotor neuropathies (McLeod and Tuck, 1987; Ewing, 1988).

The differences between control and affected animals were not large, a result expected from the experimental design. It was possible to characterize the changes in baroreceptor function in animals which had few to no signs of peripheral neuropathy. A greater degree of baroreceptor dysfunction would have resulted from the production of overt neuropathy. This was unnecessary considering the aims of the present study.

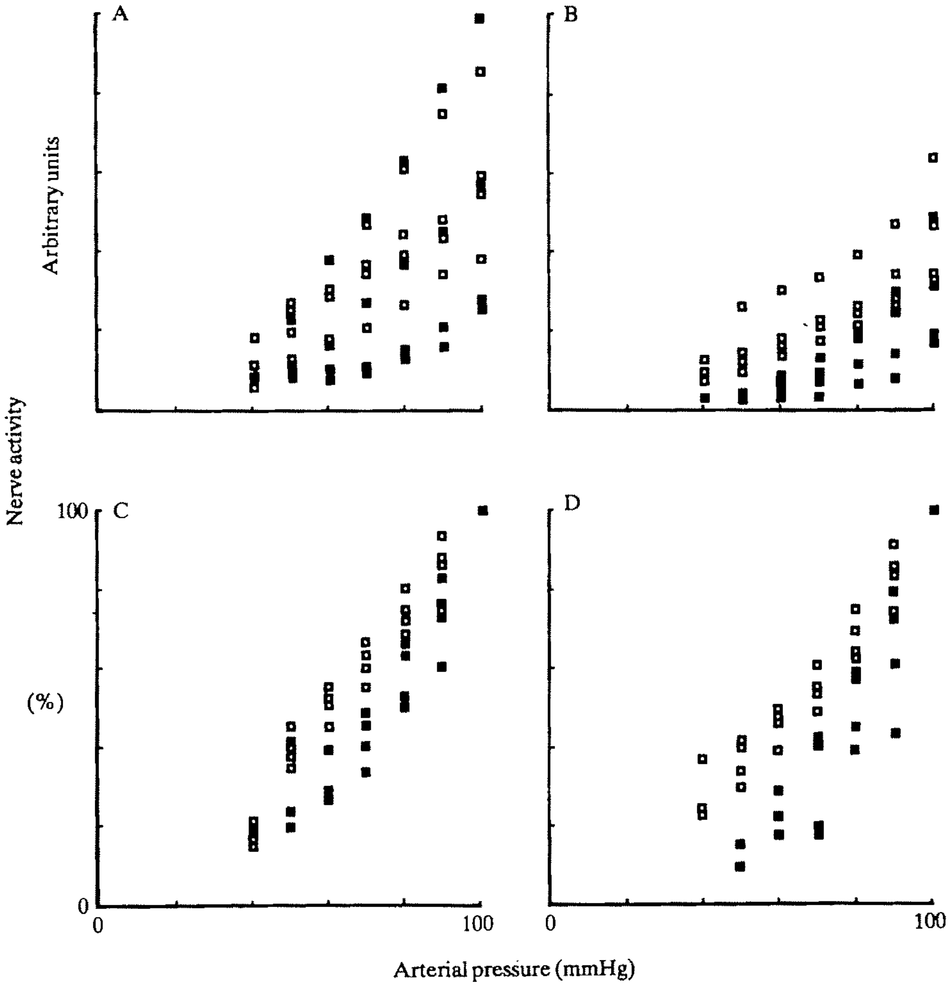

FIG. 3. A comparison of the areas of averaged baroreceptor neurograms for control (open squares) and acrylamide (closed square) animals. A, C, carotid sinus nerve; B, D, depressor nerve. In the upper panels the averaged neurograms have not been normalized and there is overlap in the amount of carotid sinus nerve activity in the two groups of animals. The amounts of depressor nerve activity do not overlap up to an arterial pressure of 80 mmHg. In the lower panels the averaged neurograms have been normalized and there is no overlap in the amounts of activity of both baroreceptor nerves up to an arterial pressure of 80 mmHg.

The depressor nerve was more damaged than the carotid sinus nerve. Depressor nerve discharge was impaired over a considerable part of the normal range of arterial pressure. In addition, the thresholds of the aortic baroreceptors were elevated. One explanation for this result is that some baroreceptor fibres had ceased to function, particularly the larger ones which innervate baroreceptors with lower thresholds and higher firing rates (Brown *et al.*, 1978). Reducing firing rates and elevated thresholds might have reflected the continuing function of a different population of baroreceptors. However, in acrylamide neuropathy damage to the slowly adapting mechanoreceptor itself can produce an identical

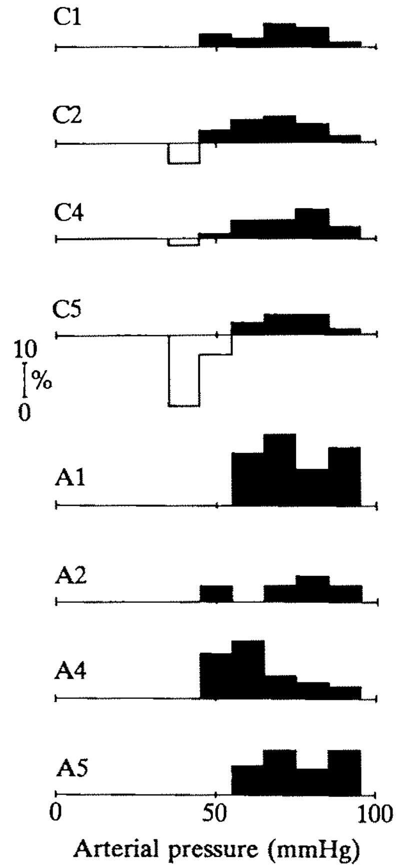

FIG. 4. A comparison of the differences in the amount of normalized nerve activities in the two groups of animals. The differences at each level of arterial pressure were obtained by subtracting the percentage of depressor nerve activity from the percentage of carotid sinus nerve activity (from fig. 3, C, D). The percentage differences between normalized carotid sinus and depressor nerve activity was significantly greater in the affected animals. In 3 of the control animals there was more depressor nerve activity than carotid sinus nerve activity at low pressures (open histograms below the line).

effect, namely an increase in threshold and a relative reduction in firing rate (Satchell and McLeod, 1984; Hersch *et al.*, 1986; Satchell, 1988). It is likely that the same changes occurred in the baroreceptors in the present study and that one factor causing abnormal baroreceptor firing was due to dysfunction of the receptor itself.

While dysfunction of the baroreceptor alone can only be proved by single fibre studies, it is likely that this abnormality was present. This type of abnormality, raised receptor thresholds and relatively reduced firing rates, have been observed in baroreceptors in hypertensive animals, a process called the 'resetting' phenomenon (Aars, 1968; Angell-James, 1973; Coleridge *et al.*, 1981). The simplest explanation for similar baroreceptor abnormalities in hypertensive animals and neuropathic animals which were not hypertensive (personal unpublished observations) is that ionic disturbances across the excitable membrane of the receptor are common to both the hypertensive (Brown, 1980) and the neuropathic baroreceptor. A more complete understanding of this type of abnormality in the baroreceptor awaits the complete identification of the ionic abnormalities across the excitable membranes in axonal neuropathies (Brismar and Tegnèr, 1984).

Although all baroreceptor nerves were damaged in the present study, the shorter carotid sinus nerve baroreceptors appeared less affected, particularly at higher arterial pressures (*see* fig. 3A, B). This relative sparing of the more cranially situated baroreceptors has been observed previously (Satchell, 1984, 1989). Two consequences follow from this observation. First, the earliest abnormality in baroreflex buffering ability should occur during declines rather than elevations from normal blood pressure levels. This may well reflect a contribution from unmyelinated baroreceptor fibres. In distal axonal neuropathies the relative sparing of the carotid sinus nerves should result in sufficient baroreceptor buffering ability for normal blood pressure control. Secondly, disturbance of carotid sinus baroreceptors during general neck or carotid artery surgery in patients with distal axonal neuropathies should be minimized as blood pressure control in this group may well be subserved by only half the normal number of baroreceptors. In particular, blood pressure fluctuations induced by manipulation of the carotid baroreceptors may not even be sensed by thoracic arterial baroreceptors.

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RECOVERY OF VOLUNTARY MOVEMENT IN HEMIPLEGIC PATIENTS

CORRELATION WITH DEGENERATIVE SHRINKAGE OF THE CEREBRAL PEDUNCLES IN CT IMAGES

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SUMMARY

The severity of the disorder of voluntary movement in 89 chronic hemiparetic patients was correlated with the degenerative reduction of descending fibres evaluated by the magnitude of the shrinkage of the cerebral peduncles (CP) in computed tomographic (CT) images. The severity of hemiplegic posture and motor disturbance in the proximal and distal muscles was related to the total amount of residual descending fibres in the CP. In all patients whose CPs were less than 60% of the normal size, recovery from disturbance in reaching and grasping movements and impairment of relative independent finger movements was incomplete. Recovery of these movements occurred when more than 60% of the CP was spared and the degree of recovery from motor weakness was positively correlated with the quantity of intact fibres spared (residual CP ratio). The ability to perform fine and discrete movements with the fingers, known to be an essential function of the pyramidal system, was consistently impaired in patients with severe shrinkage involving the medial division of the CP. There was no particular correlation between the CP shrinkage and neurological signs such as spasticity, hyperreflexia, and pathological reflexes.

INTRODUCTION

Recovery of disturbed motor function following from a cerebral lesion causing hemiparesis ceases in less than a year. Some functions recover rapidly but others remain as permanent motor deficits. It is commonly observed that recovery of impaired motor function varies depending on the location of the brain lesion and, in contrast to the proximal muscles, volitional movements of the fingers hardly improved in the first year of hemiplegia (Twitchell, 1951; Brunnstrom, 1970; DeJong, 1979). On pathological examination, however, it is difficult to attribute specific motor deficits to a specific system or location of brain lesion. The difficulties lie in the time lag between the time of clinical examination and autopsy and, except for rare cases, hemiplegic lesions inevitably involve both pyramidal and nonpyramidal systems. On the other hand, by evaluating shrinkage of the cerebral peduncles (CP) in CT images, an analysis of the

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secondary degeneration of descending fibres at the time of clinical examination became possible (Warabi *et al.*, 1987). This method enabled us to estimate the location and degree of damage to descending fibres and to correlate them with the motor disturbances observed in hemiplegic patients. In the present study, we have attempted to evaluate quantitatively both motor disturbance and shrinkage in different portions of the CP. Furthermore, we have tried to establish the neurological correlates of functional disturbances in using the fingers that persist in most hemiplegic patients by comparing the symptoms with similar motor disorders observed in monkeys when lesions were made in the pyramidal tracts (Bucy *et al.*, 1966; Lawrence and Kuypers, 1968*a*, *b*; Lawrence and Hopkins, 1976; Hepp-Reymond and Wiesendanger, 1972; Hepp-Reymond *et al.*, 1974).

SUBJECTS AND METHODS

We analysed clinical symptoms and CT images of more than 1000 hemiplegic patients and selected 89 patients; 27 healthy subjects were also studied in the same manner. All subjects volunteered to participate in the present physiological tests. Selection criteria for the patients were: (1) chronic hemiparesis for more than 1 yr; (2) strokes limited to one side and unilateral lesions on CT; and (3) absence of apraxia, marked dementia, extensive sensory disturbances or signs of either infratentorial or spinal lesions. The age range was 43−79 (mean 67) yrs. The control group consisted of healthy subjects aged 32−79 (mean 69) yrs.

The detailed method of evaluating the principal site of atrophy of descending tracts in chronic hemiplegic patients by CT scanning has already been described (Warabi *et al.*, 1987). CT slices of 5 mm were obtained parallel to the orbitomeatal line with a Toshiba TCT-80A CT scanner. The border between the CP and tegmentum was drawn as a straight line connecting the sulcus for the oculomotor nerve to the lateral sulcus. The areas of the whole midbrain, the CPs and the tegmentum were determined by the same computer program. We then calculated the ratio of the residual CP area to that of the contralateral CP (intact side).

The CP was divided into three divisions, as originally suggested by Bucy *et al.* (1964): medial fourth, central half, and lateral fourth. We then evaluated the regional CP shrinkage as previously described (Warabi *et al.*, 1987). CP shrinkage shown by CT was classified into three groups: no definite shrinkage in any division (Score 0); a small shrinkage of less than half of a division (Score 1); a large shrinkage of more than half of a division (Score 2).

The degree of motor disturbance in each hemiplegic patient was assessed with respect to hemiplegic postures, paretic limb or body movements, grip strength, and precision grip with the fingers.

Hemiplegic postures were examined in relation to the degree of elbow flexion, wrist pronation and finger flexion. Each of these abnormal postures was evaluated by more than one examiner and classified into three categories suggested by Twitchell (1951): marked hemiplegic posture (Grade 2), mild but definite hemiplegic posture (Grade 1), and no hemiplegic posture (Grade 0).

Detection of hemiparesis was made by observing the dyssynergia of reaching and grasping movements originally suggested by Twitchell (1951), Lawrence and Kuypers (1968*a*, *b*), and Brunnstrom (1970). Paretic finger movements were classified into the following three subgroups. Patients with a severe motor disturbance (Grade 2) were unable to hold a pencil with the thumb and index finger; those with a mild motor disturbance (Grade 1) were able to hold a pencil, but with some difficulty and prolonged effort; those with slight or no motor disturbance (Grade 0) were able to do this without difficulty. Paretic arm movements were also classified into three subgroups. Patients with a severe motor disturbance (Grade 2) were unable to extend the arm up to shoulder level; with a mild motor disturbance (Grade 1), they were able to do this; with slight or no motor disturbance (Grade 0), they were able to develop a full extension movement of the arm higher than shoulder level. Paretic trunk movements were again classified into three subgroups in the following way. Patients with a severe motor disturbance (Grade 2) were unable to stand even when supported by others; those with a mild motor disturbance (Grade 1) were able to stand only when supported by others or when holding on to the frame of the bed; those with slight or no motor disturbance (Grade 0) were able to stand without support from others.

Hand grasping force was measured in order to detect muscle weakness. Measurements were repeated 3 times on the normal and the hemiplegic sides in each patient. In order to study finger motor function the precision grip test was employed. A force transducer (N11-FA5-12011, NEC) was embedded in a disc with a diameter of 3 cm. Patients were asked to press the disc with the thumb and index finger in a precision grip manner as described by Hepp-Reymond *et al.* (1974). The precision grip test was performed in a reaction time paradigm. Patients were requested to press the disc as fast and as forcefully as possible in response to a buzzer sound (duration 120 ms). The interval between the onset of the auditory signal and the time when the precision grip force first attained 100 g was defined as the reaction time (in ms). Measurements were repeated 8 times on both paretic and nonparetic sides in each patient. To avoid fatigue effects, care was taken to give the patients enough rest between measurements. In order to detect more adequately the relationship between the residual CP ratios and the forces, the reactive grasping force and precision grip force were calculated as a ratio of the value of the hemiplegic side to the value of the normal side. The two-tailed t test was employed to detect statistical differences between the two sides. EMG recordings were also made from the first interosseus and thenar muscles.

RESULTS

CP shrinkage and general neurological findings

Since all the hemiplegic patients selected for the present analysis had had their stroke more than 1 yr previously, CT images of the CPs and the clinical findings on examination reflected secondary degeneration in the CP and the recovery of motor function after the acute stage. The regional shrinkage of the CPs is closely related to the extent and degree of damage to the descending tracts (Warabi *et al.*, 1987). Cerebral lesions in the anterior corona radiata or the anterior limb of the internal capsule caused a shrinkage of the medial CP (fig. 1A); lesions in the central corona radiata or the genu and the posterior limb of the internal capsule caused a shrinkage of the central CP (fig. 1B); finally, those affecting the posterior corona radiata or the posterior limb of the internal capsule caused a shrinkage of the lateral CP (fig. 1C).

Among the 89 patients with a history of hemiplegia, obvious weakness of the upper extremity was present in 97%. A spastic hemiparesis was seen in 85%, a flaccid hemiparesis in 10%, and hyperreflexia in 85%. The plantar response was extensor in 82%. No specific correlation was found between the occurrence of these clinical features and the extent and location of CP shrinkage in CT images.

Hemiplegic trunk, arm and finger movements

The relationships between the residual CP ratios (the ratios of residual CP to the intact CP in CT images) and the grades of motor disturbance for trunk, arm and finger movements are shown in fig. 2. For trunk, arm and finger movements, the data points for Grade 0 and Grade 2 disturbance aggregated around the residual CP ratios of 0.8 and 0.5, respectively. For trunk movements, the residual CP ratios had wide distribution for all the three grades, suggesting that the motor disturbance in trunk movement was relatively independent of CP shrinkage (fig. 2, Trunk). However, the degree of motor

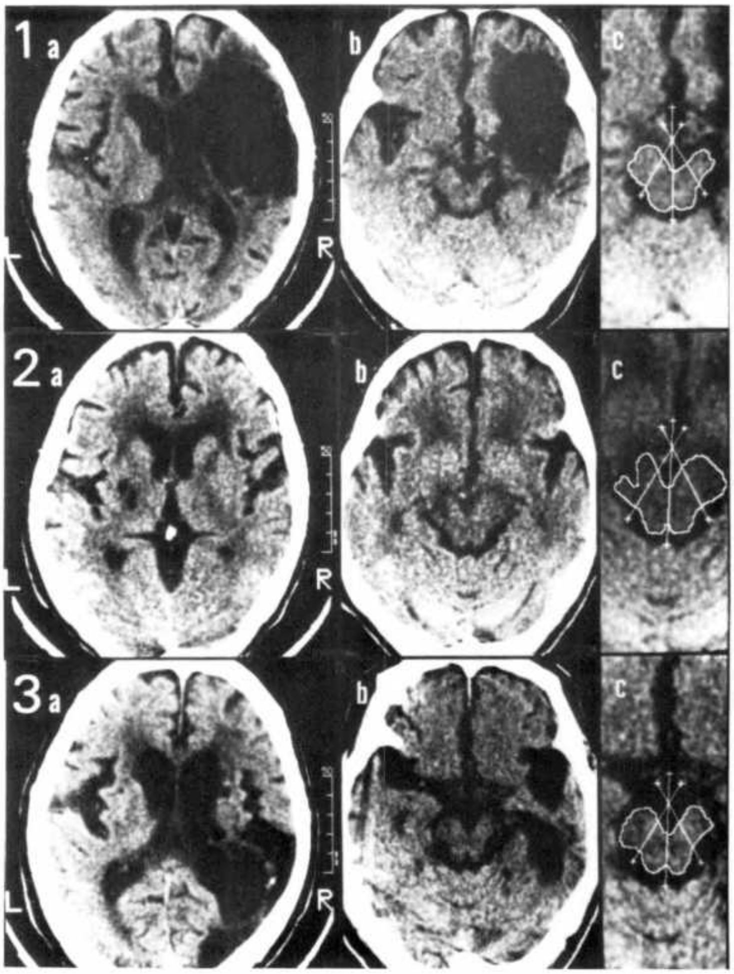

FIG. 1. CT demonstrations of partial and marked shrinkage of the midbrain. 1, 72-yr-old patient with a 5 yr history of left hemiplegia. A low density area in the frontal lobe (a, b) accompanied shrinkage (b, c) of the medial CP scored Medial 2, Central 1, Lateral 1 (2, 1, 1). The residual CP ratio was 0.57 of that on his normal side. 2, 71-yr-old patient with a 3 yr history of hemiplegia. A small low density area involving the posterior limb of the internal capsual (a) is associated with shrinkage (b, c) in the central CP scored Medial 1, Central 2, Lateral 1 (1, 2, 1). The residual CP ratio was 0.61 of that on his normal side. 3, 64-yr-old patient with a 5 yr history of left hemiplegia. A low density area in the parietal, occipital and temporal lobes (a) was accompanied by shrinkage (b, c) in the lateral CP scored Medial 1, Central 1, Lateral 2 (1, 1, 2). The residual CP ratio was 0.71 of that on his normal side.

disturbance of arm movements was closely correlated with the size of residual CP (fig. 2, Arm). The correlation was more pronounced for finger movements (fig. 2, Fingers).

Fig. 3 shows relationships between the residual CP ratios and the regional CP shrinkage scores in relation to the grades of arm and finger disturbance. For trunk movements, the site of regional CP shrinkage had no clear relationship with the grade of motor disturbance (data not shown). But the degree of motor disturbance of arm and finger movement was related to the site of shrinkage when the residual CP was more than

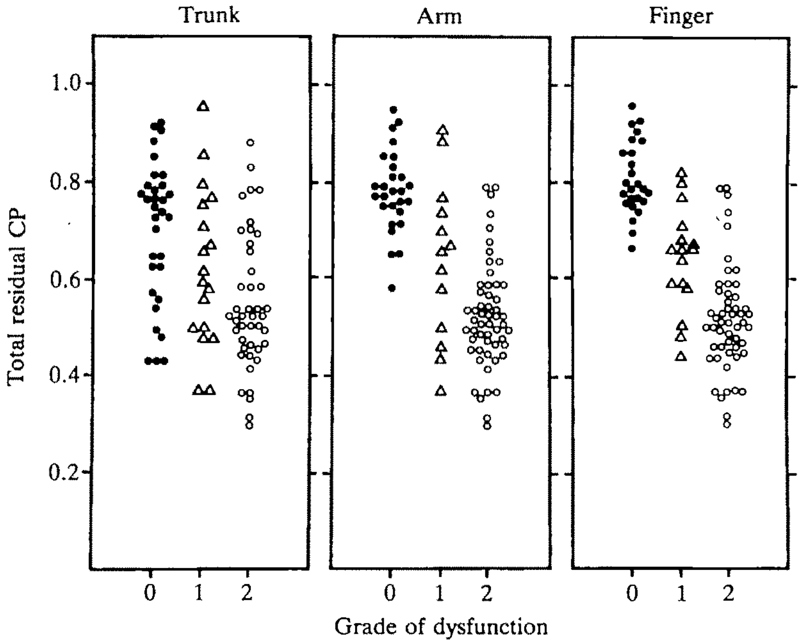

FIG. 2. Relationships between the severity of hemiplegic disturbances and the total residual CP ratios for trunk, arm and finger movements. Closed circles = slight or no motor disturbance (Grade 0); open triangles = mild motor disturbances (Grade 1); open circles = severe motor disturbances (Grade 2). For trunk movements the mean residual CP ratio for Grade 0 patients was 0.68 and that for Grade 2 was 0.57. For arm movements the mean residual CP ratio was 0.80 for Grade 0, 0.64 for Grade 1, and 0.53 for Grade 2 patients. For finger movements the mean residual CP ratio was 0.82 for Grade 0, 0.64 for Grade 1, and 0.51 for Grade 2 patients. In contrast to the disturbance of trunk movements, the severity of arm and finger motor disturbances showed a higher correlation with the residual CP ratios.

0.6. In patients possessing extensive CP medial Score 2 lesions (fig. 1A), recovery from the motor disturbance was poor. With regard to the regional differences in arm and finger movements, it was noteworthy that all the patients with medial Score 2 showed a marked motor disturbance of Grade 2, except for 1 case with Grade 1 motor disturbance for the fingers (fig. 3B, Medial). In contrast, the mean grades of motor disturbance in patients with Score 2 shrinkage either in the central or lateral CP (figs 1B, 3) and the residual CP is more than 0.6, were around 1.0, indicating that recovery from the disturbance was relatively favourable (fig. 3, Central, Lateral).

Hemiplegic posture

In general, typical forms of hemiplegic posture seen in the upper extremity were elbow flexion, wrist pronation and finger flexion. However, every patient did not necessarily show all these postures. Elbow flexion was seen in 53% of the patients, while finger flexion was observed in 63%; 70% (62 patients) showed either one of these abnormal postures or both. The frequency of occurrences of these was obviously related to the degree of CP shrinkage; the smaller the residual CP ratio, the higher was the incidence

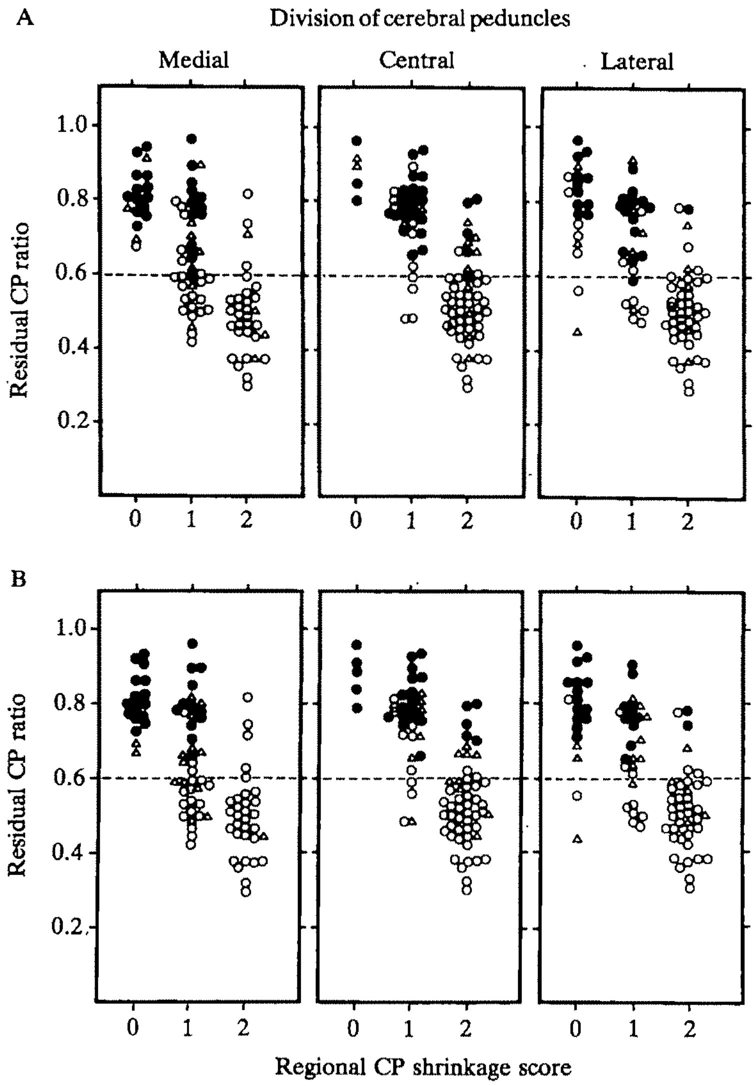

FIG. 3. Relationships between the total residual CP ratios (ordinate) and the regional CP shrinkage scores (abscissa) in relation to the grades of disturbance of arm (A) and finger movement (B). The regional shrinkage scores are shown for each division of the CP. The severity of motor disturbances is indicated by the same symbols as in fig. 2, Arm. The recovery of motor function in the arm and finger movement was related to the residual CP ratio, and to the regional shrinkage score for the medial CP. The minimum values for the residual CP ratio were 0.58 and 0.66 for Grade 0 arm and finger movements, respectively. Recovery from motor disturbances of the fingers was good in the patients showing a residual CP 0.66 or higher, while considerable disturbance persisted in most patients with a residual CP ratio <0.60. Symbols as in fig. 2.

of hemiplegic posture (fig. 4). When the residual CP ratio was less than 0.4 (fig. 4), the patients all showed elbow flexion, wrist pronation and finger flexion. No regional differences in CP shrinkage were found to correlate with flexed elbow posture (fig.

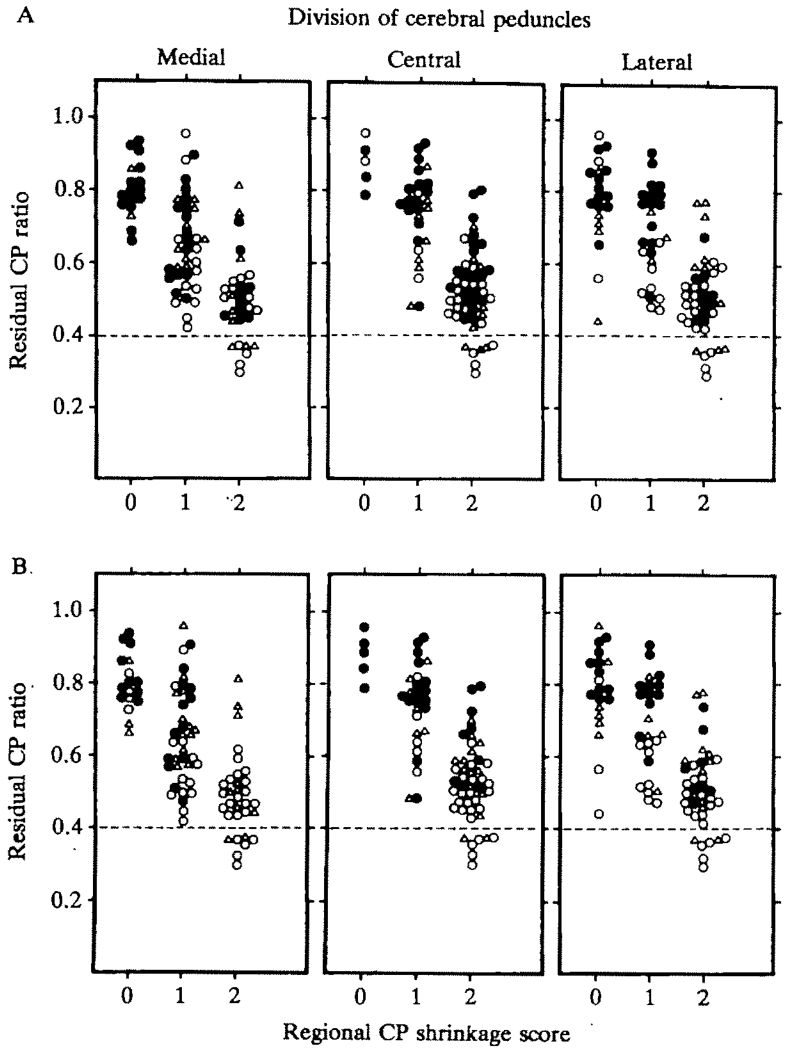

FIG. 4. The severity of hemiplegic elbow (A) and finger (B) postures in relation to the residual CP ratios (ordinate) and regional CP shrinkage scores (abscissa). Degrees of hemiplegic elbow and finger postures are represented by different symbols: closed circles = unaffected cases (Grade 0); open triangles = cases with mild hemiplegic postures (Grade 1); open circles = cases with severe hemiplegic postures (Grade 2). Three scores of regional CP shrinkage were determined for the 3 divisions of the CP. A Score 2 shrinkage for the medial CP was exhibited most frequently by patients with finger flexion postures.

4A). A finger flexion posture was observed more frequently among patients with extensive shrinkage in the medial CP (fig. 4B, Medial).

Analysis of grasping force

Muscle weakness was analysed by measuring grasping force. The relation between grasping force and residual CP size is given in fig. 5A. Fig. 5B shows that relative grasping force is significantly correlated with the residual CP size (correlation coefficient

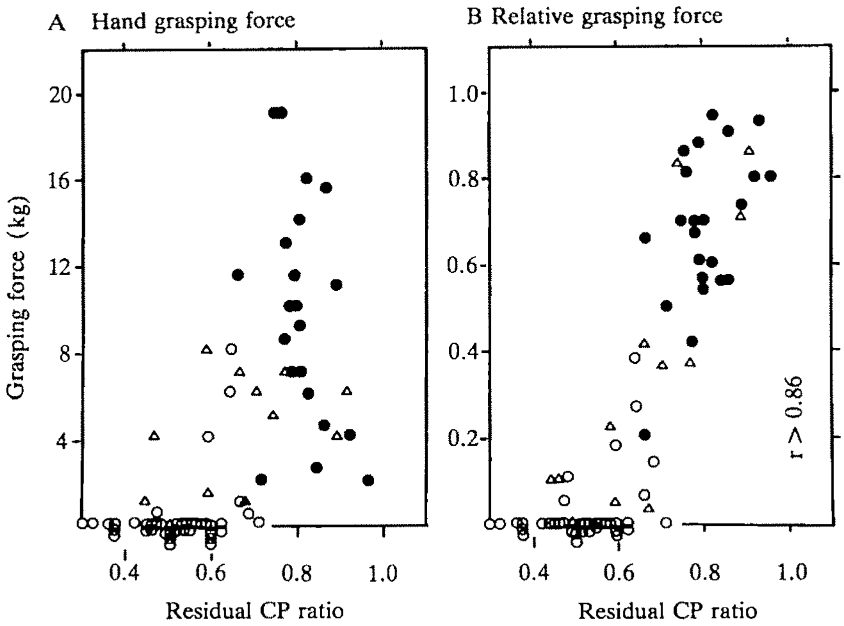

FIG. 5. A, relationships between the absolute grasping force and the residual CP ratio. B, relationships between relative grasping force and residual CP ratio. Each symbol represents a patient and his grade of motor disturbance for the arm. Closed circles = slight or no motor disturbance (Grade 0); open triangles = mild motor disturbance (Grade 2); open circles = severe motor disturbance (Grade 2). The grasping force measured on the hemiplegic side ranged from 0 to 8 kg in patients with a Grade 2 arm disturbance, from 1 to 8 kg in Grade 1 and 2 to 19 kg in Grade 0 patients (A). The residual CP ratio was significantly correlated ($r > 0.86$) with the relative grasping force, assuming grasping force of the normal side to be 1 (B).

$r = 0.86$). It also illustrates that relative grasping force is smaller among patients with a greater motor disturbance in the arm.

Precision grip test

Reaction times and time course of force development in the performance of the nonaffected side of hemiplegic patients were essentially similar to those in the normal control subjects. The EMG on the unaffected side also was normal in that it displayed typical triphasic burst discharges at the initial phase of muscle contraction followed by a tonic discharge period. On the paretic side, generally the number of motor units recruited in the EMG was decreased and the triphasic pattern at movement onset was less distinct or absent (data not shown). The reaction time was often increased as compared with the unaffected side. The increase was statistically significant ($P < 0.05$, two-tailed t test) in 11 of 29 tested cases (Table). The peak force attained in the precision grip with the affected fingers was significantly less than that for the unaffected side in 27 of 29 tested cases ($P < 0.05$, *see* Table). Not only the peak force but also the time course of force development were generally different, as shown in fig. 6 (compare trace in the right column a, b and c with those in A, B and C).

TABLE. MEAN VALUES FOR PRECISION GRIP REACTION TIME AND PEAK FORCE

	Normal side Mean (SD)	*Affected side Mean (SD)*	*Case with significant difference (P < 0.05)*	
Average reaction time (ms)	344 (162)	498 (381)	11/29 (Extend)	0/29 (Shorten)
Average peak force (kg)	2.68 (1.61)	1.15 (1.04)	27/29 (Weaken)	

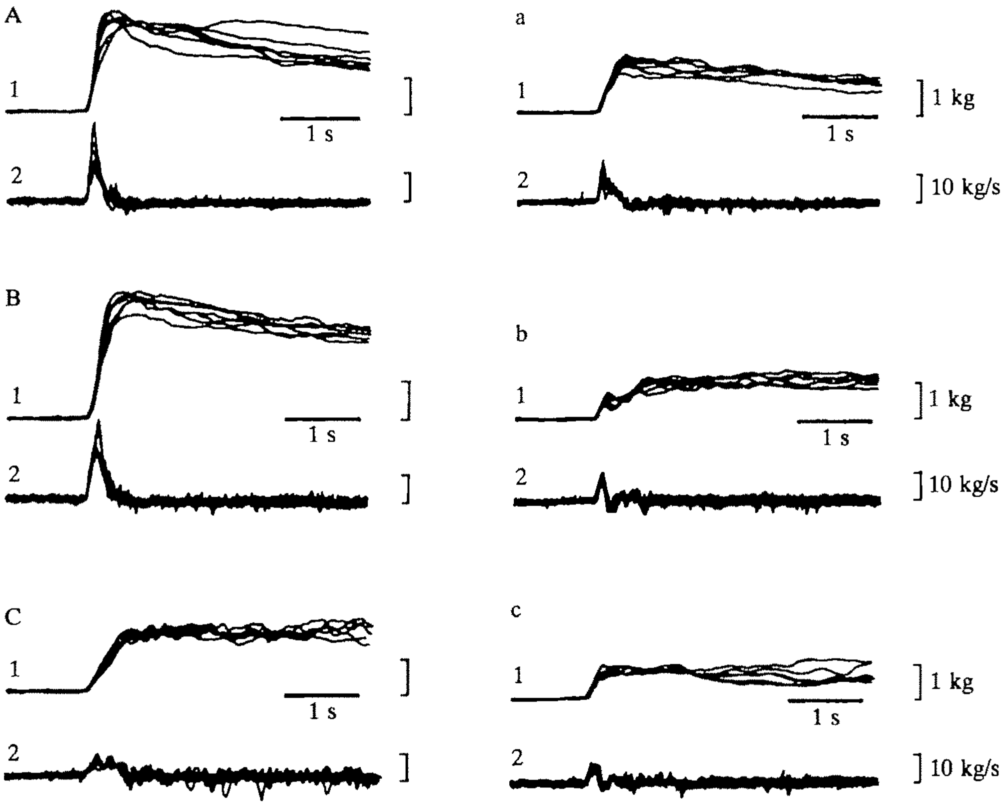

FIG. 6. Precision finger grip force on the normal (*left*) and the hemiplegic side (*right*). Three hemiparetic patients (normal side: A, B, C; affected side: a, b, c) are shown. 1 = precision grip force; 2 = differentiated precision grip force. Recordings of 6 responses are superimposed after aligning them at the onset of the precision grip. Peak force decreased on the affected side (a, b, c). In contrast to the normal side, a short peak time (a), an extended peak time (b) or mixed peak time (c) were observed on the affected side.

An attempt was made to correlate grip force of the affected side with the residual CP size. Owing to the large variation between individual patients, grip force itself appeared to show no correlation, as indicated in fig. 7A. However, when the relative value (expressed as the ratio to the grip force of the unaffected side) was correlated, there was a positive correlation with residual CP size (r = 0.52, fig. 7B). Fig. 7B also

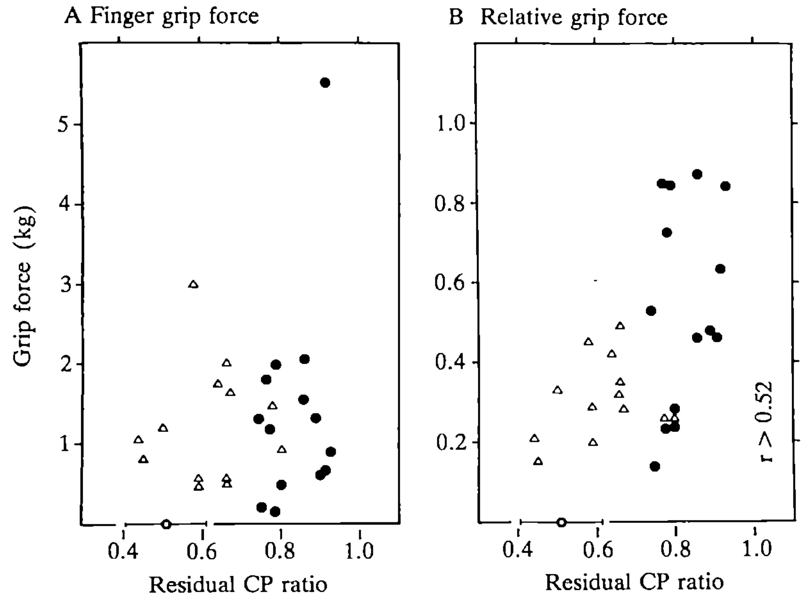

FIG. 7. Relationships between the precision grip force (abscissa) and the residual CP ratios (ordinate). In A, absolute grip force and in B, relative grip force are represented on the ordinates. Each symbol indicates a hemiparetic patient and his grade of motor disturbance in the fingers. Closed circles = slight or no motor disturbance (Grade 0); open triangles = mild motor disturbance (Grade 1); open circles = severe motor disturbance (Grade 2). The relationships between the relative grip force and the residual CP ratio are correlated ($r > 0.52$). The average residual CP ratio for which grip forces of Grade 1 were less than 100 g is represented by a double circle on the line of the abscissa; bar = SD.

shows that patients classified as having a mild motor disturbance of the fingers (Grade 1) exhibited a relative grip force of less than 0.5, whereas the value exceeded 0.5 in half of them.

DISCUSSION

The present study confirmed the commonly stated notion that recovery from hemiplegia first occurs and is most complete in proximal muscles, while voluntary movements of the hand and fingers recover last, are weaker, and much more severely affected as far as dexterity is concerned (Twitchell, 1951; Brunnstrom, 1970). The analysis of brain lesions in CT images disclosed that severe impairment in the ability to perform fine and discrete actions with the fingers was closely associated wtih a reduction in fibres descending in the medial division of the CP. In patients showing a considerable diminution of the medial division of the CP in CT images, the typical hemiplegic symptoms such as flexed posture of the fingers, disturbances in reaching and grasping actions, and difficulty in fine and discrete actions of the fingers, were always observed.

Results from animal experiments have shown that the fine and discrete actions of the fingers are the essential motor function of the pyramidal system. When the pyramidal tracts were interrupted, monkeys showed a severe disturbance in independent movements of the distal parts of the limb, especially the hand, and a permanent loss of individual finger movements (Tower, 1940; Lawrence and Kuypers, 1968*a*, *b*; Lawrence and Hopkins, 1976; Hepp-Reymond and Wiesendanger, 1972; Hepp-Reymond *et al.*, 1974). In these monkeys, however, movements of the trunk and combined body-limb movements were unaffected. Similar motor disturbances have also been demonstrated in monkeys when lesions of the pyramidal tracts were made at the level of the CP (Bucy *et al.*, 1964, 1966). Bucy *et al.* (1966) reported disturbances in the usefulness of the hand and fingers as a result of damage to the medial division of the CP that were added to central CP lesions. It is important to note that clinical signs in hemiplegic patients such as spasticity, exaggeration of the tendon reflexes or extensor plantar responses were not observed in monkeys whose lesions were confined to the pyramidal system (Fulton and Keller, 1932; Tower, 1940). As brain lesions causing hemiplegia commonly included both the pyramidal and nonpyramidal systems, the spasticity and exaggeration of the tendon reflexes observable in hemiplegic patients may be attributed to damage to nonpyramidal pathways. On the other hand, the results from pyramidotomized monkeys suggest that the permanent impairment of relatively independent finger movements, found as one of the persistent motor disturbances in hemiplegic patients, is most probably the result of injury to the pyramidal system. The present analysis of CT images showed that the impairment was particularly notable in patients with shrinkage of the medial division of the CP. Although we were unable to determine whether fibres responsible for relatively independent finger movements actually descend in the medial CP, or fibres which serve to compensate for the damaged physiological pathways descend in the medial CP, the findings of the present study, together with those of the animal experiments, indicate that the fibres which descend in the medial CP play a crucial role in fine and discrete movements of the fingers and that these movements are controlled most probably by the pyramidal system.

The number of residual descending fibres in the CP determined the degree of recovery of the hemiplegic posture and motor weakness. The typical hemiplegic posture of elbow flexion, flexion and pronation of the wrist, and finger flexion, was always seen in patients with a marked CP shrinkage (residual CP ratio less than 0.4). Because the substantia nigra was included in the area which we termed the CP in CT images, the actual area occupied by descending fibres was only 68% of the CP (Warabi *et al.*, 1987). In a patient with residual CP ratio of 0.4, therefore, 88% (60/68) of the descending fibres had been lost. A typical or a partial hemiplegic gait and a posture with a flexed upper extremity and extended lower extremity were commonly seen in patients with a small residual CP ratio (0.4–0.6). Thus CT images confirmed the view that the typical hemiplegic posture is produced by extensive damage of the fibres descending in the CP.

It is generally agreed that the various motor functions are controlled by different networks of motor fibres (Truex and Carpenter, 1964; Lawrence and Kuypers, 1968*a*, *b*; Brodal, 1981). The results from pyramidotomized monkeys have shown that motor weakness is correlated with the number of intact descending fibres but not with the location of the damage in the pyramid (Barnard and Woolsey, 1956; Beck and Chambers, 1970). The present clinical observations confirmed that recovery from motor weakness is dependent on residual CP ratio. In patients with a residual CP ratio of less than 0.6 (equivalent to the loss of approximately 58% (40/68) of the descending fibres), full recovery of motor function to the level of Grade 0 did not occur and the patient was not able to hold a pencil. Damage to approximately 60% of the descending fibres appears to be the critical level in determining recovery of precision grip finger movements in hemiplegic patients. When the residual CP ratio was greater than 0.6, it was evident that recovery of muscle strength was dependent on the total number of residual descending fibres, including the corticospinal, corticobulbar, corticoreticular and corticopontine tracts, and a number of other small fibre bundles. Both grasping force and precision grip force were related to the number of residual descending fibres. Thus our results in hemiplegic patients are in agreement with the experimental data (Barnard and Woolsey, 1956; Beck and Chambers, 1970) and indicate that the severity of motor weakness for gross hand movements such as grasping depends on the total extent of descending fibre loss in the whole of the CP. However, the force of and the ability to perform isolated precision grip movements seems to depend not only on the total number of residual descending fibres but also on those localized within the residual CP. The impairment of finger movements was therefore not related to muscle weakness but to the hemiplegic flexion posture of the fingers and 'stiffness' in individual finger movements. Furthermore, when the residual CP ratio was greater than 0.6, the values of grasping force and residual CP were positively correlated ($r = 0.86$, *see* fig. 5B). When a similar analysis was made between the values for precision grip force and residual CP ratio, the correlation coefficient was only 0.52, indicating that recovery of fine and discrete actions of the fingers does not depend simply on the total reduction in descending fibres. These neurological findings and the CT images would indicate that the recovery of relatively independent finger movement depends largely on the damage to specific fibres descending in the medial division of the CP. Thus recovery of the motor function of relatively independent finger movement, which is known from animal experiments to be a unique and essential function of the pyramidal system, differs from recovery of the other gross movements of the hand, arm and proximal muscles. Recovery of the latter appears to depend simply on the number of residual nonspecific fibres descending in the entire CP.

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PERIPERSONAL AND VERTICAL NEGLECT

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SUMMARY

When bisecting radial lines visually, normal subjects err towards distant peripersonal space, and when bisecting vertical lines visually, they err towards upper vertical space. In contrast, when bisecting lines under tactile-proprioceptive guidance, subjects err towards near peripersonal space, suggesting that normally attention is preferentially distributed away from the body during visual exploration but distributed towards the body during tactile exploration. A patient with ischaemic lesions, however, involving both inferior temporal lobes neglected far peripersonal and upper vertical space. He also demonstrated a motor bias away from the neglected space. These findings suggest that in man attention is spatially directed in three orthogonal axes (horizontal, vertical and radial), that attention may normally be unequally distributed in each of these axes, and that neglect may occur in not only the horizontal axis but also in the radial and vertical axes.

INTRODUCTION

An individual with neglect fails to respond to novel or meaningful stimuli despite the preservation of elementary sensory and motor functon (Heilman *et al.*, 1985*b*). Neglect has been attributed to deficits both in attentional and intentional (motor preparatory) processes. The behavioural manifestations of neglect are usually most profound in extrapersonal and body space contralateral to hemisphere lesions, most often left hemispace as defined by the midsagittal plane. Head and body midline are important determinants of the neglected spatial field, and the visual half-field has relatively less influence (Bowers *et al.*, 1981; Heilman *et al.*, 1987).

Several observations, however, suggest that neglect may occur in other fields of extrapersonal space and therefore that attentional-intentional processes may be organized in a more complex manner. First, many subjects with left hemispatial neglect fail to cancel most targets in the left lower quadrant (Morris *et al.*, 1985). Secondly, extinction and neglect of stimuli in the lower visual fields have recently been reported in man (Rapcsak *et al.*, 1988). Finally, neglect of pericutaneous stimuli has been reported in monkeys (Rizzolatti *et al.*, 1983). We recently evaluated a man for multimodal neglect of upper space and distant extrapersonal space and compared him with 12 control subjects.

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METHODS

Subject

A 66-yr-old right-handed white man with an eighth grade education who worked as a house painter was transferred to the Veterans Administration Medical Center in Gainesville, Florida, from an outside hospital following a stroke. He experienced the sudden onset of headache, visual loss, and right-sided weakness in the evening, and the following morning he was found to be blind with mild left-sided paresis and decreased arousal. His deficits improved over several days, and he was left with inconsistent visual field loss and a severe anterograde amnesia. The aetiology of his stroke was presumed to be embolic from a cardiac source; mitral annulus calcification but no thrombus was demonstrated on echocardiography. He had a pacemaker inserted for atrial fibrillation and sinus pauses of 2–3 s and he was maintained on digoxin, quinidine, verapamil and warfarin.

Six weeks after his stroke he was alert and cooperative but distractable, with motor impersistance for eye closure and arm extension. He was generally hypokinetic, and there was a paucity of spontaneous speech. Language was fluent with good repetition and naming. Comprehension of conversational speech was normal but he had some difficulty with complex sequential commands. He was disorientated for time and place, had a severe anterograde amnesia for verbal and figural material, and a relatively extensive retrograde memory deficit extending 20 yrs into the past. Verbal fluency was 1 item in 60 s; praxis, simple calculations, right/left orientation, and finger recognition were normal. Insight, general knowledge, vocabulary, abstract reasoning and problem solving were compatible with his educational and occupational level. He had a stable bilateral upper hemivisual field loss, which was complete except for the ability to detect and localize light. Pursuit eye movements in all directions were broken into small saccades. Visual function improved to the point where he was able to discriminate high contrast gratings with a period of less than 30 min arc, and he localized target dots of less than 12 min arc diameter. Optokinetic nystagmus was elicited with 25 min arc gratings to right, left and upward stimuli, resulting in downward saccades. He traced drawings of standard line widths with his right index finger but was unable to identify figures on the usual charts for estimating visual acuity. He accurately localized all light stimuli under visual guidance for targets in the lower visual fields by reaching out with his right hand, but made a systematic error towards the lower right when reaching for targets in the upper visual fields. His error was 3–4 cm for targets in the right upper quadrant and 30–40 cm for targets in the left upper quadrant. He was aware of his errors and perplexed by them. To isolate the effect of spatial field on reaching behaviour, target location in the visual field was controlled by having the patient fixate the target. When fixating targets placed in various spatial fields, he accurately localized them in lower hemispace (below eye level) but made systematic errors in reaching for targets in upper hemispace (fig. 1). He was unable to differentiate relative line

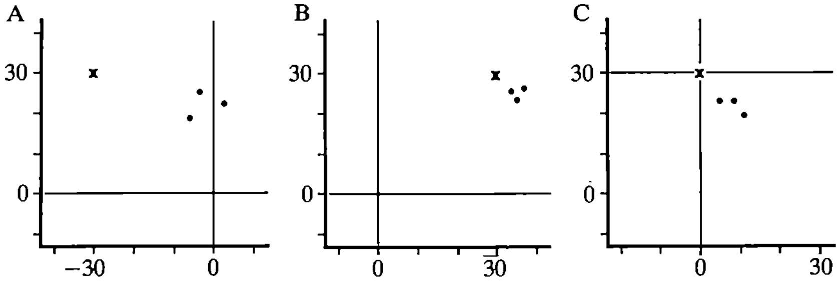

FIG. 1. Visual mislocalization by reaching for a point of light (A) viewed in left upper visual quadrant, 30 cm above eye level; B, viewed in right upper visual quadrant; and C, fixated 30 cm above eye level. x = target; dots = response; zero vertical displacement is eye level, zero horizontal displacement is body midline. The intersection of coordinate lines indicates the point of visual fixation in each case.

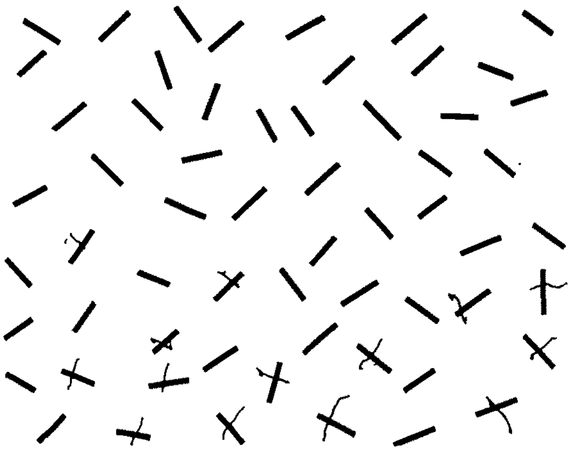

FIG. 2. Line cancellation task presented free-field on desk top (transverse plane), 30 cm from body surface.

orientations of less than 90° but could differentiate circle size differences of 2 mm. A complete description of his apperceptive visual agnosia, colour agnosia, and prosopagnosia will be reported elsewhere.

This man demonstrated left hemispatial neglect on line bisection and cancellation tasks (fig. 2). In addition, he failed to cancel targets in the upper quadrants and misbisected vertical lines below midpoint. He neglected upper and left portions of drawings, in copying figures and in tracing, but completed them when the stimulus figures were inverted. Numbers clustered in the right lower quadrant of his drawing of a clock (fig. 3).

He had mild bilateral paratonic rigidity ('Gegenhalten'), worse on the right, and mild weakness of the right deltoid and triceps and left upper extremity generally. The tendon reflexes were brisk in the left upper and lower extremities and the plantar responses were extensor bilaterally. There was mild dysmetria and intention tremor in the left arm, and he had mildly decreased proprioception in the fingers of the right hand. There was, however, no dysmetria in the right arm as evidenced by normal finger-nose testing with eyes closed. Crude sensation, tactile object and number recognition, and tactile and proprioceptive point localization on the body and in space were normal as he was able to locate the opposite hand in space

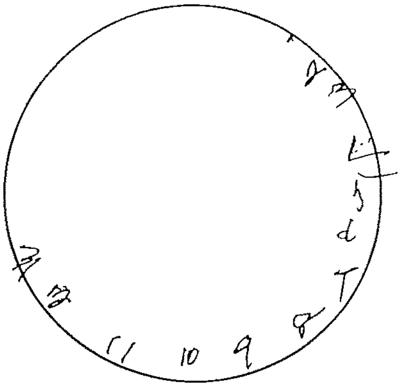

FIG. 3. Drawing of clock.

with eyes closed. CT scans documented the evolution of bilateral inferior temporal lobe and deep occipital lobe ischaemic infarction, worse on the left, but no evidence of parietal lobe pathology (fig. 4).

He was seen in follow-up 6 months after his first evaluation. At this time his visual acuity was testable with a Snellen eye chart because of improvement in number recognition, and his acuity had improved to 20/100 in the right eye and 20/200 in the left. His visual field had enlarged to approximately 60° above the horizontal meridian at their maximum using moving or stationary solid targets, but varied in size from day to day. On some days he had only 20° of vision in the superior visual quadrants, and he demonstrated significant fatigue over the course of each testing session such that a region of visual inattention for stationary stimuli gradually replaced the visual extinction in upper visual fields, and finally no visual function could be documented above the horizontal meridian at the end of the test session on some days. Upper visual quadrant extinction was clearly demonstrated for stimuli (90° movement of the examiner's index finger) presented simultaneously in upper and lower visual quadrants in each of the right and left hemifields. Right-sided tactile extinction was present, and right visual extinction was demonstrable only for stimuli presented simultaneously in both superior quadrants. There was no extinction of peripheral targets when central and peripheral stimuli were presented simultaneously in the lower visual fields. Testing for extinction of distal versus proximal stimuli in peripersonal space was more difficult and limited by the degree of preserved superior quadrant vision. Nonetheless, on some occasions an upper visual field stimulus was no longer extinguished when presented 30 cm closer to the subject's face than a simultaneous stimulus in the lower visual quadrant. Visual mislocalization toward the lower right was still present but of lesser degree.

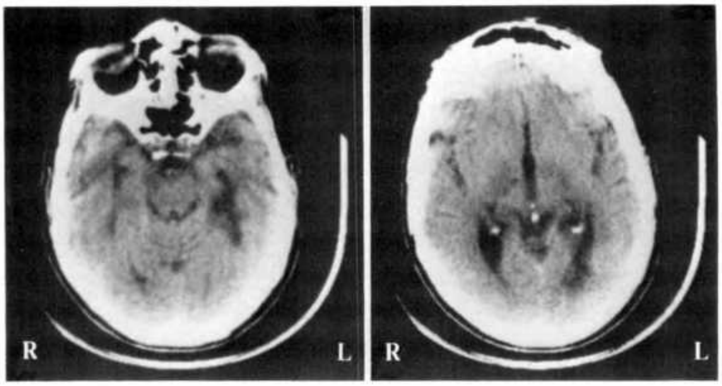

FIG. 4. CT scan at the level of A, inferior temporal lobes, and B, calcarine cortex 6 weeks poststroke, revealing hypodense lesions in posterior medial temporal lobes (fusiform and lingular gyri), left greater than right, and dilated occipital horn of the left lateral ventricle.

Controls

There were 12 control subjects, 8 male and 4 female. Eight were selected from the orthopaedic and internal medicine inpatient service (controls 1–8) after excluding active central nervous system disease, a past history of stroke, seizures, dementia, malignancy, major psychiatric disorder, or evidence of decreased arousal or neglect on screening neurological examination. The mean age of the hospital controls was 57 yrs and their mean educational level was 10 yrs. Four healthy volunteers also participated (controls 9–12) and had a mean age of 35 yrs.

To evaluate the nature of this patient's neglect more fully, his performance was tested using a line bisection task under a variety of spatial conditions, and we compared his performance with that of control subjects.

Apparatus and procedures

Subjects were asked to bisect single black lines of 2.5 mm width and of six different lengths (20, 22, 24, 26, 28, 30 cm), and centred on a 21.6×35.5 cm page (visuomotor condition). Stimuli were presented in blocks of 12 trials, 2 of each length, in a pseudorandomized fashion. Stimuli were located in 12 different areas of egocentric extrapersonal space for the patient, along 3 orthogonal axes (fig. 5). Horizontal lines were presented in the usual fashion with pages in the transverse plane flat on a tabletop and with lines orientated along the intersecting frontal (coronal) plane 30 cm in front of the subjects (horizonal condition).

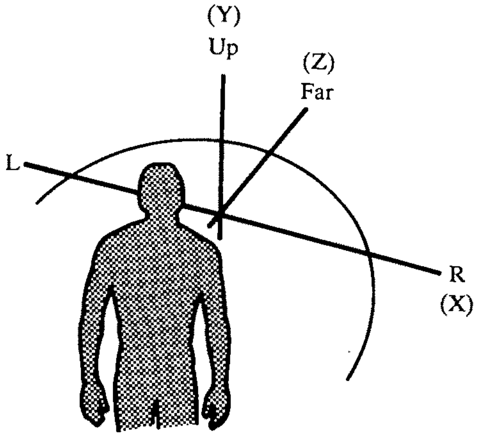

FIG. 5. The region of egocentric extrapersonal space studied; stimuli aligned along three orthogonal axes.

Vertical lines were presented on pages 30 cm in front of the subjects at the intersection of the frontal and midsaggital plane (vertical condition). Radial lines were presented on pages in the transverse plane at table level with lines orientated along the intersection of the midsagittal plane (radial condition). Stimuli were placed in 3 locations along the horizontal axis: with midpoint approximately 30 cm right, 30 cm left, or at the midline. Stimuli were also placed in 3 locations along the radial axis: with pages adjacent to the body surface (near), with the line midpoint approximately 30 cm (middle), or 60 cm (far condition) from the subject; and in 6 locations along the vertical axis, from 15 cm above eye level to 60 cm below eye level. Three blocks of 12 trials were presented in each radial location, and one block of 12 trials were presented in the horizontal and vertical locations. The order of presentation of blocks of trials was counterbalanced to control for the effects of practice and fatigue, and test sessions were limited to 1 h. It was required that the subject explore the full extent of the test line before attempting to bisect it, there was no time limit for completion of the task, and he/she was reminded of the instructions when necessary.

A tactuomotor line bisection task was given to the subjects by using wooden rods of 2.5 mm width and again of 6 lengths (20, 22, 24, 26, 28, 30 cm). One block of 12 trials was presented in each of the following locations: far-radial, eye level vertical, and right and left-horizontal. The subject's index finger was placed on the end of the rod, and he was instructed to explore the rod and find the midpoint while blindfolded. Again, the subject was required to explore the full extent of the stimulus and to identify both ends of the rod before attempting to bisect it. They were started at one end of the rod in half of the trials and at the opposite end in the other half, the order of the starting point being varied pseudorandomly.

The test procedures for the controls were the same as for the patient except that only one block (12 trials) was presented in each of 6 locations for the visuomotor task: near and far space along the radial dimension, right and left hemispace, and at eye level and 30 cm below eye level in the vertical dimension. Rods were presented in 4 locations for the tactuomotor task: near, far, eye level, and 30 cm below eye level. In addition to the noncued line bisections in the visuomotor condition, both the patient and the control subjects were presented with an equal number of cued line bisections where subjects were required to name letters at the line ends before performing the bisection to document that the subject had attended to the entire line.

Analysis

Visual line bisection error was measured to an accuracy of ±1 mm from the true midpoint, and the mean error and SD in cm were calculated for each condition. Tactile bisections were measured to an accuracy of 0.25 cm. The direction of the error along each dimension was arbitrarily assigned a (+) or (−) value. Errors to the right of midpoint of horizontal lines, above the midpoint of vertical lines, and beyond the midpoint of radial lines, were assigned (+) values whereas errors to the left, below, or near the midpoint for radial lines were given (−) values. To facilitate interpretation of the results, the definition of egocentric extracorporeal space was elaborated to specify regions of space with particular relevance in terms of behaviour. Extracorporeal space was divided into peripersonal space, within arm's reach, and extrapersonal space, beyond arm's reach. Peripersonal space was further divided into near space, immediately adjacent to the body surface, middle and far peripersonal space. Location may be specified in a polar coordinate system, along a radius extending from body centre and orientated at a given angle from the anterior midsagittal line in a plane transverse to the long axis of the body. Such a system does not diminish the importance of bilateral symmetry in the concept of extracorporeal space but radial distance from the individual may influence performance independently within a given hemispace.

The mean line bisection error (LBE) in cm was calculated for each block of trials for both patient and controls across the 5 bisection tasks (visual-vertical, visual-radial, visual-horizontal, tactile-vertical, tactile-radial). The control data from these 5 tasks were analysed using repeated measures analysis of variance (ANOVA). For all analyses, the mean LBE was compared with zero (i.e., the actual midpoint) by constructing a null set of data.

Separate ANOVAs were performed for the 3 visual bisection tasks, using Position (eye level vs below eye level for the vertical task; near vs far for the radial task; left vs right for the horizontal task); and Cue (cued, uncued), and Data (actual, null) as within-subject factors. Separate ANOVAs were also performed for the two tactile tasks using Position (eye level vs below eye level for the vertical task; near vs far for the radial task) and Data (actual, null) as the within-subjects factors.

The mean age of the control group was 1 SD less than the age of the patient (66 yrs); the control group was therefore divided into subjects older (n = 5) and younger (n = 7) than 55 yrs. The mean age of the older group was 65.4 yrs (SD = 8.73), and the two groups were compared by ANOVA. As there was no significant difference in LBE between the young and older control subjects on any of the 5 tasks just described, the data for the whole control group were pooled for subsequent comparisons with the patient.

RESULTS

As shown in Table 1, for the 3 visual line bisection tasks, results of the ANOVAs indicated that controls significantly misbisected radial [F(1,11) = 19.63, *P* = 0.001] and vertically placed lines [F(1,11) = 36.38, *P* = 0.0001], whereas horizontal lines were not significantly misbisected [F(1,11) = 2.96, *P* = 0.11]. All remaining effects and interactions were nonsignificant, that is, cueing did not affect bisection performance across any of the spatial conditions [radial: F(1,11) = 2.11, *P* = 0.17; vertical: F(1,11) = 1.26, *P* = 0.28; horizontal: F(1,11) = 0.02, *P* = 0.90]. The data from the two conditions were pooled for each location in subsequent analyses. There was a trend for vertically presented lines to be more accurately bisected when positioned below eye

TABLE 1. LINE BISECTION ERROR: MEAN OF 12 CONTROL SUBJECTS

	Mean (cm)	*SD*	*t**	*P value*
Visual				
Near	0.65	0.66	3.26	<0.01
Far	0.90	0.66	4.54	<0.001
Eye level	0.75	0.42	5.95	<0.0001
Below	0.54	0.40	4.52	<0.001
Tactile				
Near	−0.09	0.68	−0.40	n.s.
Far	−0.92	0.99	−2.78	<0.05
Eye level	−0.34	1.42	−0.72	n.s.
Below	−0.38	1.11	−1.03	n.s.

* One sample, two-tailed t test, df = 11. (+) values for LBE beyond midpoint (radial) or above midpoint (vertical); (−) values for LBE near midpoint or below midpoint.

level (X = 0.54 cm, SD = 0.40) than when positioned at eye level (X = 0.75, SD = 0.42), indicating a gradient of response similar to that seen in hemispatial neglect [F(1,11) = 4.60, $P = 0.055$].

The control group's means for the 2 tactile bisection tasks (vertical, radial) are presented in Table 1. Results of the ANOVAs indicated that control subjects significantly misbisected radially positioned lines [F(1,9) = 11.12, $P = 0.0087$]. In addition, there was a trend for radial lines in near peripersonal space to be more accurately bisected than lines in far peripersonal space [F(1,9) = 3.47, $P = 0.095$], indicating another gradient of response like that observed in hemispatial neglect. No significant main effects or interactions were observed in the vertical tactual line bisection task [F(1,9) = 1.02, $P = 0.034$].

Finally, the visual and tactile bisection tasks were directly compared for each spatial condition (radial, vertical) in separate ANOVAs. In both conditions, Modality (visual, tactile) and Position (near vs far radial, eye level vs below eye level vertical) were the within-subject factors. In these analyses, only the uncued visual data (as there was no cued condition in the tactile tasks) and data from the 10 subjects completing both visual and tactile tasks were used. The visual and tactile LBE for all subjects are presented in figs 6 (radial) and 7 (vertical). Results of these analyses indicated a significant difference in bisection performance between the two modalities in both the radial [F(1,9) = 21.81, $P = 0.0012$] and vertical conditions [F(1,9) = 8.39, $P = 0.018$]. The LBE was of equal magnitude in each modality in far peripersonal space but in opposite directions. There was a significant Modality×Position interaction [F(1,9) = 5.15, $P = 0.049$], and post hoc comparisons using Tukey HSD revealed that visual far radial differed significantly from the tactile far radial LBE ($P < 0.05$). Together, these results indicate that normal subjects err toward the body on tactuomotor but away from the body on visuomotor radial line bisections and that the error is of greatest magnitude in far peripersonal space. Even though no significant vertical tactuomotor LBE was demonstrated, normal subjects also erred in a consistent fashion upwards or away from the body on the vertical visuomotor task.

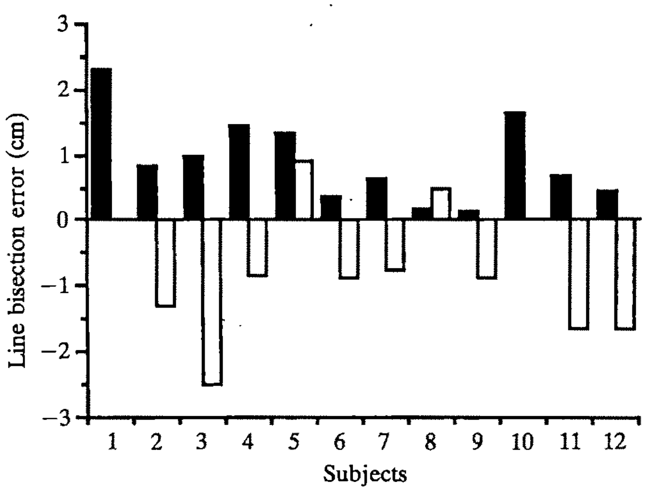

FIG. 6. Mean line bisection error of 12 control subjects for radial stimuli in visuomotor and tactuomotor conditions. (+) error beyond, (−) error near midpoint. Closed bars = visual; open bars = tactile.

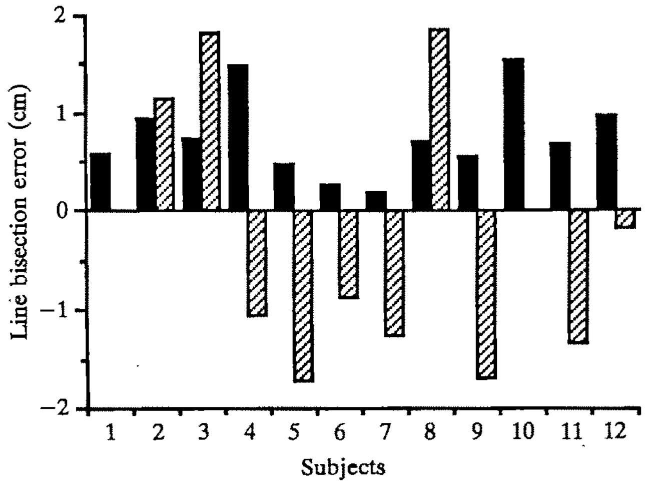

FIG. 7. Mean line bisection error of 12 control subjects for vertical stimuli in visuomotor and tactuomotor conditions. (+) error above, (−) error below midpoint. Closed bars = visual; hatched bars = tactile.

As shown in Table 2, the patient's mean LBE was compared with zero (no LBE) using a one sample, two-tailed t test. To control for the effect of multiple t tests, the patient data were adjusted with Bonferroni's inequality. The patient repeated the bisection procedure in 12 conditions, and the P values reported in the table have been adjusted to $P \times 12$. The patient's mean error in each condition was compared with the controls by calculating the number of SDs from the sample mean. The patient misbisected horizontal lines to the right of midline in the visual condition (midline location:

TABLE 2. LINE BISECTION ERROR: PATIENT DATA

		Visual				*Tactile*			
Condition	*Location*	*Mean*	*SD*	*t**	P_c	*Mean*	*SD*	*t**	P_c
Horizontal	Left	1.18	1.59	2.58	n.s.	4.17	1.93	7.46	<0.0002
	Midline	1.88	1.00	6.52	<0.001	–			
	Right	−5.56	1.88	−10.26	<0.0001	−1.54	2.07	−2.58	n.s.
Radial	Near	−2.34	1.49	−0.46**	<0.000001	–			
	Middle	−5.33	2.35	−13.59**	<0.000001	–			
	Far	−7.10	1.95	21.85**	<0.000001	−2.74	2.13	−4.46	<0.02
Vertical	+15†	−5.78	2.08	−9.62	<0.0001	–			
	EL	−5.66	2.20	−8.89	<0.0001	−2.73	3.16	−2.99	n.s.
	−15	−1.04	1.96	−1.84	n.s.	–			
	−30	−2.98	2.23	−4.63	<0.01	–			
	−45	−2.59	2.03	−4.41	<0.02	–			
	−60	−1.18	2.13	−1.91	n.s.	–			

* One sample, two-tailed t test, df = 11; ** df = 35. † cm above (+) or below (−) eye level. (+) values for LBE beyond midpoint (radial), above midpoint (vertical) or the right (horizontal); (−) values for LBE near of midpoint or below midpoint; EL = eye level; P_c = Bonferroni adjustment $P \times 12$.

X = 1.88 cm, SD = 1.00; left hemispace: X = 1.18 cm, SD = 1.59) but erred to the left for stimuli located in right hemispace (X = 5.56, SD = 1.88). The LBE was significant at midline (t = 6.52, $P < 0.001$) and in right hemispace (t = 10.26, $P < 0.001$). His error was greater than 3 SD from the control sample mean for stimuli in left hemispace and 15 SD in right hemispace, indicating a significant degree of left hemispatial neglect and, at least for stimuli more peripheral in the right hemispatial field, a degree of right hemispatial neglect. He manifested only left hemispatial neglect in the tactuomotor condition (X = 4.17, SD = 1.93, $P < 0.001$) and only with stimuli in left hemispace.

There is no horizontal plane for separating upper from lower hemispace that is comparable with the midsagittal plane that separates right from left hemispace. When the eyes are in neutral position, the midsagittal plane also separates the right visual field from the left. Therefore we chose eye level as the plane to separate upper from lower hemispace because when the eyes are in neutral position this plane separates upper from lower visual fields. In the visual modality the patient erred consistently below the midpoint of vertical lines (eye level: X = 5.66 cm, SD = 2.20 cm, $P < 0.0001$; 30 cm below eye level: X = 2.98 cm, SD = 2.23, $P < 0.01$) and was 15 SD from the control mean at eye level. He demonstrated a gradient of response such that LBE was of greatest magnitude for stimuli in upper vertical space as defined by eye level. In the tactuomotor condition, he erred below midpoint (X = −2.73, SD = 3.16) but with the conservative estimate of significance used (the Bonferonni adjustment), it failed to reach statistical significance (t = −2.99, $P < 0.12$).

Finally, the patient consistently misbisected radial lines towards his body at all distances in both visual and tactile modalities. In far peripersonal space in the visual modality he erred by a mean 7.10 cm (SD 1.95 cm, $P < 0.000001$) and in the tactile modality by 2.74 cm (SD 2.13 cm, $P < 0.012$). In near space in the visual modality he misbisected radial lines by a mean 2.34 cm (SD 1.49 cm, $P < 0.000001$). He again demonstrated a gradient of response with greater directional errors for more distant stimuli. His LBE was greater than 4 SD from the mean of the controls in both near and far visual conditions and 1.8 SD from the controls in the tactuomotor condition.

DISCUSSION

The patient described here demonstrated left as well as a degree of right hemispatial neglect on a cancellation task and on line bisection. In addition, he clearly demonstrated extinction of visual stimuli (finger flexion) presented to either superior visual quadrant with simultaneous lower quadrant stimulation. The errors in line cancellation over the top half of the page and in copying figures are analogous to the exploratory and constructional deficits seen in hemispatial neglect and suggest neglect of upper vertical space. When stimuli viewed in the superior visual field were brought near the patient, they were no longer extinguished when presented simultaneously with distant lower visual field stimuli, suggesting neglect of more distant stimuli in the superior visual fields. Retinal image size, however, is a major determinant of depth perception, and this study did not allow us to determine which factor is the most relevant. Near stimuli may also be qualitatively different than far stimuli, and these differences may have accounted for our results. He misbisected vertical lines below and radial lines near midpoint under both visual and tactile control. His errors were consistent and differed significantly from those of the control subjects, suggesting neglect of upper vertical and far peripersonal space.

Because hemianopic patients do not necessarily have neglect and many patients with neglect are not hemianopic, loss of elementary visual function cannot itself account for these deficits in spatial behaviour (Rosenberger, 1974; Ogden, 1985). The patient traced relatively complex figures and had no difficulty in tracing single lines whose extent was limited to the right inferior visual quadrant. His errors and his failure to explore the material were consistently related to the spatial and visual field in which the stimulus was located. Therefore, whereas neglect may have influenced his visual recognition and contributed to his agnosic errors, his visual and perceptual deficits cannot totally account for the line bisection error in upper space. Furthermore, there is no reason to suspect that upper visual field loss would affect line bisection performance more than hemianopia does.

Elementary motor deficits cannot explain the patient's response bias as all testing was done with the right hand. There was only minimal weakness in the right arm in a pattern that cannot be ascribed to his stroke, and limb movement throughout the field where stimuli were located was unrestricted. As he was required to explore the full extent of test lines before tactile bisection, clearly he was able to reach midpoint in all cases. For far radial stimuli the response was always further from the body than the true midpoint of near or midradial lines, indicating that his responses fall short of midpoint for a reason other than restriction of basic motor function. Similarly, in the cued visual bisection task, the identification of figures at the line ends proved that the full extent of the line had been perceived before bisection.

A pathophysiological substrate for vertical neglect has not been entirely elucidated. The patient with lower altitudinal neglect previously reported (Rapcsak *et al.*, 1988) had bilateral parieto-occipital lesions, whereas this patient had bilateral inferior temporo-occipital lesions. As indicated by Rapcsak *et al.* (1988), the upper hemiretina has physiological superiority, and lower visual field stimuli may be more successful in competing for limited attentional capacity. Subjects with a global decrease in visual spatial attention capacity may therefore manifest upper visual inattention because of the comparatively greater saliency of lower visual field stimuli. This alone, however, cannot account for the multimodal nature of vertical neglect in these 2 patients. Electrophysiological studies in monkeys have demonstrated the existence of populations of light-sensitive inferior parietal (IPL) neurons with visual receptive fields confined to upper or lower visual quadrants (Robinson *et al.*, 1978; Motter and Mountcastle, 1981). Some cells with quadrantic receptive fields include the fovea, and this class generally discharged to a light stimulus in that quadrant or their activity was further enhanced by saccades towards the light stimulus. Recording from IPL, Robinson *et al.* (1978) demonstrated a preponderance of receptive fields in the lower contralateral visual field, and Motter and Mountcastle (1981) found that cells in IPL, active during hand manipulation, had visual receptive fields confined to the lower quadrants. These cells appear similar in other respects to IPL neurons which are proposed to mediate the direction of attention (Mountcastle, 1976). The paucity of cells with upper quadrant visual receptive fields identified in area 7a suggests that neurons with these 'attentional' properties may be located elsewhere. If so, the inferior temporal visual association cortex might contain such cells.

In addition to his vertical neglect in cancellation, line bisection, and drawing tasks, our patient demonstrated misreaching and consistently erred to the lower right. He not only misreached for targets in upper visual half-fields but also in upper hemispace, irrespective of the retinotopic location of the stimulus. Although he had a mild proprioceptive deficit in the digits of the right hand, there was no dysmetria and he was able to localize his opposite limb accurately in space when blindfolded. A proprioceptive deficit alone should not cause a consistent directional error. Furthermore, this task requires an open-loop movement on the first trial in any location and requires proprioceptive information from both the passively positioned as well as the actively exploring limb (DeJong, 1988). Point localization through the use of proprioceptive information was preserved, therefore misreaching was due to a defect in visually-guided motor behaviour. Holmes (1918, 1919) studied visual localization in patients with bilateral brain injury and found that localization was defective throughout the visual fields. Subsequently, however, cases with defective visual localization restricted to the left or right homonymous visual half-fields were described (Riddoch, 1935; Brain, 1941; Bender and Teuber, 1947). Some patients were consistent in the direction of error (Poppelreuter, 1917) but others were not (Cole *et al.*, 1962; Ratcliff and Davies-Jones, 1972). Subjects with acute lesions characteristically misjudged direction (localization in a frontal plane) and distance (localization in radial direction) but patients with chronic deficits reported by Ratcliff and Davies-Jones (1972) erred only in direction. When subjects who misreach directed their gaze peripherally so as to fixate peripheral targets, Cole *et al.* (1962) found that the misreaching disappeared. On this basis they concluded that visual disorientation was due to a visual perceptual defect and not to motor guidance per se (reaching). However, Levine *et al.* (1978) reported a case with inaccurate reaching due to a tumour of the superior parietal lobule of the right hemisphere. When the target was fixated but the left hand could not be seen, misreaching persisted. If the subject, however, was allowed to view the left hand as it approached its goal, misreaching disappeared altogether. It appears that the deficit was in the cross-modal integration of proprioceptive and visual information about spatial location.

Unlike these previous cases, our patient mislocalized targets when he was allowed to view his hand both in the upper hemifield and in upper hemispace when the targets above eye level were fixated. Accurate reaching for fixated targets in lower hemispace indicates that the spatial field of the target had an independent influence on visually-guided reaching behaviour. Visual mislocalization was systematically towards the lower right, away from the upper and left spatial fields where he manifested spatial neglect. A similar but horizontal motor bias, termed directional hypokinesia, has been demonstrated in patients with neglect from isolated parietal lobe lesions (Valenstein *et al.*, 1982; Heilman *et al.*, 1985*a*). Activation of movements towards the neglected field is decreased and manifests as delayed initiation of movement towards neglected space as well as a tendency to fall short of the target (Meador *et al.*, 1988). The pattern of mislocalization demonstrated by this man may be due to directional hypokinesia and a function of the attentional-intentional mechanisms rather than a visual perceptual disturbance per se.

Unlike the patients of Cole *et al.* (1962) and Levine *et al.* (1978) whose mislocalization disappeared for peripheral targets visualized in the central visual field, mislocalization persisted in the central visual field in our case but was less severe. This amelioration of misreaching in central vision could represent the same kind of improvement demonstrated by the previously reported patients and which was believed to support the supposition that visual disorientation is due to a defect in visual perception. The dependence on spatial field of stimulus demonstrated here, however, is characteristic of attentional processes. A hemispace-visual field interaction has been demonstrated for visual extinction whereby stimuli located more peripherally in the visual field are neglected to a greater degree (Rapcsak *et al.*, 1987). In addition, neglect is most profound when visual half-field and head and body hemispace coincide (Bowers *et al.*, 1981). Directional hypokinesia therefore appears to be the most plausible explanation for misreaching in this man. It remains unclear to what extent intentional or visual spatial neglect may account for misreaching and visual disorientation in general, as previous studies have failed to control for hemispace. Directional hypokinesia may actually be a frequent cause of misreaching but would appear to be restricted to cases with systematic directional errors.

Ventre *et al.* (1984) proposed that visual mislocalization and motor aspects of hemispatial neglect are related phenomena, 'the two syndromes overlap and are part of the same functional, if not anatomical, entity'. Further, they proposed that both syndromes may result from a displacement of an egocentric coordinate system relative to allocentric coordinates derived through sensory input and following a parietal lesion. The results of the current study are consistent with this hypothesis in that visually-guided localization of an external point showed a systematic directional error, whereas no such misreaching was demonstrated towards parts of the patient's own body, where location may be interpreted in terms of egocentric coordinates alone. In the tactile line bisection task, the systematic directional error reappeared, and the results can be interpreted as a displacement of the egocentric coordinate systems guiding the movement of the exploring finger relative to the accurately perceived allocentric coordinates of the midpoint of the rod. The original hypothesis of Ventre *et al.* (1984) may be explained on the basis of a failure of cross-modal integration between retinotopic location and proprioceptive information required for accurate reaching. If the response bias is due to mismatching of egocentric and allocentric coordinates then the same error should exist irrespective of sensory modality. The results of the line bisection test are consistent with the hypothesis but it is not possible to dissociate the effect of the divided attention aspect of the task.

The study of spatial neglect has emphasized the importance of contralateral hemispace in the control of behaviour. Brain (1941), however, suggested that the region of extrapersonal space within grasping distance was also of special significance. More recent studies support this contention and suggest that attentional processes mediate this bias. Leinonen *et al.* (1979) and Leinonen and Nyman (1979) showed that a population of neurons in area 7b of the parietal cortex of the monkey are multimodal and that their activity is enhanced only by visual targets approaching their cutaneous receptive field or by stationary stimuli within 5 – 10 cm of it. Most of these light-sensitive cells responded only to movement in a specific direction and did not respond at all if the target was greater than 1 m from the monkey. Area 7b projects in a unidirectional fashion to the posterior bank of the arcuate sulcus (Chavis and Pandya, 1976) and Rizzolatti *et al.* (1981*a, b*) showed that cells in this region have properties analogous to those in area 7b: 54% of the neurons responded consistently to visual stimuli only if less than 10 cm away, and 46% responded to stimuli within arm's reach. They introduced the term peripersonal space to denote this region of extrapersonal space and showed subsequently that postarcuate ablations induce visual and tactile neglect of contralateral pericutaneous stimuli and increased latency in reaching for targets in peripersonal space. Lesions in area 7b likewise result in attentional deficits limited predominantly to contralateral peripersonal space (Rizzolatti *et al.*, 1985).

In the present study we demonstrated that multimodal neglect of events in far peripersonal space occurs in man. The patient misbisected radial lines near midpoint, under either visual or kinaesthetic guidance, and there was a gradient of response whereby his error diminished as stimuli were placed nearer the body. The LBE indicates a deficit in selective attention to far space and a motor bias toward the body, that is, away from the neglected field. The attentional mechanisms in man appear to be organized in terms of proximity to the body in addition to the horizontal and vertical dimension, and focal hemisphere lesions can affect attention-intention to far space preferentially. The localization of these processes in man is unclear. Area 7 of the monkey cortex is analogous to the inferior parietal lobule of man, but lesions of this region in man have not been shown to be associated with neglect of distal stimuli. It is possible that inferior temporal structures are important in the mediation of attention to far peripersonal and upper vertical space, especially in view of the paucity of light-sensitive inferior parietal neurons with superior quadrantic receptive fields.

Lastly, attentional or intentional biases have been reported previously in normal subjects. For example, normal subjects bisect horizontal lines towards the left (Bowers and Heilman, 1980; Bradshaw *et al.*, 1983). Our control subjects also demonstrated a bias on radial and vertical line bisection. However, unlike the bias reported for horizontal lines, the radial bias was modality-specific such that with the visual task the subjects erred away from their body and with the somaesthetic task they erred towards their body. The visual system is, by virtue of the ability to sense light, specialized for detecting distant stimuli. In contrast, the somaesthetic modality is restricted to the detection of stimuli on or near the body. Perhaps with this specialization there is a modality-specific attentional bias such that attention is preferentially distributed away from the body during visual exploration but is biased towards the body during tactile exploration.

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PREMOTOR CORTEX AND CONDITIONAL MOTOR LEARNING IN MAN

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SUMMARY

The role of premotor cortex (PMC) in conditional motor learning tasks in man was investigated. Patients with PMC lesions had to learn to associate 6 different visual, tactile or auditory stimuli with 6 different arm movements which were previously rehearsed (Task A). A comparative task involved an association between the same set of sensory stimuli and 6 spatial locations (Task B). Patients with PMC lesions were only impaired when they had to recall a movement from memory on the basis of a sensory cue (Task A), but not for an association involving spatial location (Task B). This indicates that the PMC plays a role in sensory conditional motor learning.

INTRODUCTION

There is evidence both from single cell recordings and from the behavioural effects of ablation studies in monkeys that premotor areas are concerned with the conditions for action. The electrophysiological data indicate that there are neurons both in the arcuate premotor area and in the supplementary motor cortex that fire differentially in tasks where the monkeys have to choose which movement to make on the basis of a sensory instruction (e.g., Tanji *et al.*, 1980; Weinrich and Wise, 1982; Godschalk *et al.*, 1985; Wise and Mauritz, 1985).

Investigations of the behavioural effects of premotor lesions in monkeys have demonstrated severe impairments on tasks in which the animals had to learn arbitrary associations between visual stimuli and a set of motor associations. Petrides (1985*a*) found that periarcuate lesions caused a severe impairment in the learning of a motor conditional task, whereas more anterior lesions of the principalis region showed only a mild retardation. Halsband and Passingham (1982, 1985) and Halsband (1983, 1987) have shown that monkeys with premotor ablations were impaired at relearning a task in which they had to select one of two movements as instructed by a visual cue. It was found that the monkeys were impaired only when they had to recall a movement from memory on the basis of a visual cue; the same animals were able to learn a nonmotor conditional task on which the visual cues specified which object should be chosen. In this study the premotor lesions were bilateral and the animals were allowed to use their preferred hand in manipulating the handle.

In these investigations the ability of monkeys with ablations of the premotor cortex (PMC) to choose the correct movement on the basis of proprioceptive or auditory cues

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has not been examined. In one study both visual and auditory cues were presented, but the task required a choice between objects rather than a selection of the correct movement (Delacour *et al.*, 1972).

Taken together, the available data on electrophysiological and brain lesion studies in nonhuman primates suggest that the premotor areas are concerned with the conditions for action. But little attention has been paid to the role of PMC and the supplementary motor area (SMA) in conditional motor learning tasks in man. Petrides (1985*b*) examined patients with sustained unilateral damage to the frontal cortex on a visual spatial as compared with a nonspatial conditional task. His results indicate that patients with surgical excisions from the left or right frontal cortex were severely impaired in learning both tasks. The excisions of his patients involved varying amounts of the dorsolateral cortex, some of them extending medially to involve parts of the anterior cingulate gyrus.

The aim of the experiments to be described here was to analyse the performance of patients with lesions involving the PMC in sensory conditional tasks designed to be similar to those previously used with nonhuman primates. The experiments tested whether patients with PMC or SMA lesions are impaired in their ability to learn arbitrary associations between sensory stimuli and a set of motor acts or spatial locations. Furthermore, they also assessed whether there is a dorsolateral and medial dissociation and a hemisphere specialization for conditional motor learning in man. Finally, an analysis was made to establish whether a given conditional motor deficit is affected by different sensory modalities, or whether it is restricted to the usage of cues in one modality.

SUBJECTS

This study is based on 12 patients with lesions involving larger parts of the PMC, 2 patients with lesions involving predominantly the primary motor cortex (M1) and 30 healthy control subjects; 17 subjects with lesions of the parietal lobe served as additional controls. The extent of cortical damage to the parietal lobes was comparable in size to the cortical damage in our subjects with premotor lesions.

Eight of the PMC lesions were in the left and 4 in the right hemisphere. In addition, 2 patients with bilateral PMC lesions are described; they were excluded from the present learning paradigms because of severe mnestic disturbances (*see* below).

Eleven of the parietal lesions were in the left and 6 in the right hemisphere. The M1 lesions were both in the left hemisphere. The case reports and outlines of lesions of the patients with frontal lesions will be given in this article, whereas those cases with posterior lesions serving as an additional control group will be described elsewhere (Pause *et al.*, 1989).

All patients were right-handed and tested only for their dominant hand, irrespective of the side of the lesion. Testing was restricted to one hand only because of the time needed for the testing sessions. The average duration of the experiment was 8 h. In order to avoid fatigue, the experimental sessions were restricted to 90 min. Handedness was established by means of the TÜLUC ('Tübinger-Luria-Christensen') questionnaire. The handedness score was based on hand preference shown in 20 everyday situations (e.g., tooth brushing, catching a ball, etc.).

METHODS

Sensory conditional learning

Screening procedure

All patients were tested on a German version of the Wechsler Adult Intelligence Scale and two formal memory and attention tasks (SKT; Wechsler Memory Scale). Only patients with full-scale IQ ratings above 85 and below 130 who did not show evidence of a serious deficit in memory and attention were included in this study. The 2 patients with bilateral premotor lesions and 2 cases with left parietal lesions showed evidence of severe mnestic and attention deficits and were excluded from the present learning paradigms. In addition, 1 patient with right parietal lobe damage was eliminated because of neglect disturbances.

Preceding the associative learning tasks, the performance of the patients was compared with that of control subjects on 3 sensory discrimination tasks to ascertain intact discrimination of the different stimuli in each modality. This was done in order to exclude the possibility that the conditional associative learning deficits of a given patient result from a difficulty in discriminating between the sensory stimuli. All subjects were required to make successive discriminations within the visual, tactile and auditory modalities. (1) *Visual discrimination*. The subjects were required to judge whether 2 successively presented plaques were of the same or different colour. There were 10 pairs of coloured plaques: 5 pairs were of the same colour, and 5 differed. (2) *Tactile discrimination*. Using his dominant hand the patient was required to judge whether 2 objects in a pair presented in succession were identical or not. There were 10 pairs of wooden objects, comparable in weight, but differing in shape, e.g., cube, cylinder, pyramid. All objects were hidden from view, and half of the pairs were the same. (3) *Auditory discrimination*. The patient was required to judge whether 2 successively presented noises in a pair (e.g., high and low frequency tones, clapping, whistling) were the same or different. The noises were recorded on a stereotape and delivered by loudspeakers well above individual detection thresholds (>60 dB). Noises were presented at an interval of 2 s. Five pairs of successively presented noises were the same and 5 were different. It was found that all patients were able to discriminate the sensory stimuli successfully.

Experiment 1: sensory conditional motor tasks (motor selection)

The experimenter and the subject were seated at a table facing each other. At the beginning of the testing session the subject was shown 6 arm movements. Thereafter, each movement had to be reproduced by the subject using his dominant hand. A trial began with the subject copying a particular movement with his right arm; after the patient had successfully copied this movement he was presented with the next one. The subject was told after each movement if the copying was correct or not; if an error was made, another trial began with demonstration of the same movement.

The 6 movements to be performed with the subject's dominant hand were as follows: (1) with the outstretched arm a downward semicircular arc was transcribed beginning from a position to the left of the body midline and ending at a position to the right of the midline; (2) with the hand on his right shoulder unfolding it through about 90° downwards; (3) beginning with the outstretched hand positioned at the right side of the body, the arm was extended to reach an endpoint at which the arm was obliquely extended to the left of the body midline; (4) with the arm half extended, a turning movement of the hand to the right of about 45° with the palm down was executed (as in turning a door knob); (5) with the forearm horizontally extended drawing the hand towards the body; (6) with the forearm extended the hand was pushed about 30 cm downwards. Training continued until the subject made 18 consecutive correct responses involving 3 replications of each movement (fig. 1, Stage 1).

After completion of this initial stage, the subject was required to perform the movements from memory in any order (fig. 1, Stage 2). If the patient was unable to remember one or more of these movements, the experimenter demonstrated them once more, with the subject copying as before (i.e., going back to Stage 1). The patient was allowed repeats, but still had to produce the complete set of 6 hand movements 3 times in a row with no incorrect movements.

In the next stage (fig. 1, Stage 3) each of the 5 sensory stimuli that had to be discriminated before had now to be associated with one and only one of the hand movements which were previously rehearsed. The task was to find out which movement was the correct one for each stimulus. The conditional motor tasks were then also performed for the two other sensory modalities so that visual, tactile and auditory conditional motor learning were tested.

The experimental procedure was identical for the three sensory conditions. On any trial, 1 of the 6 stimuli

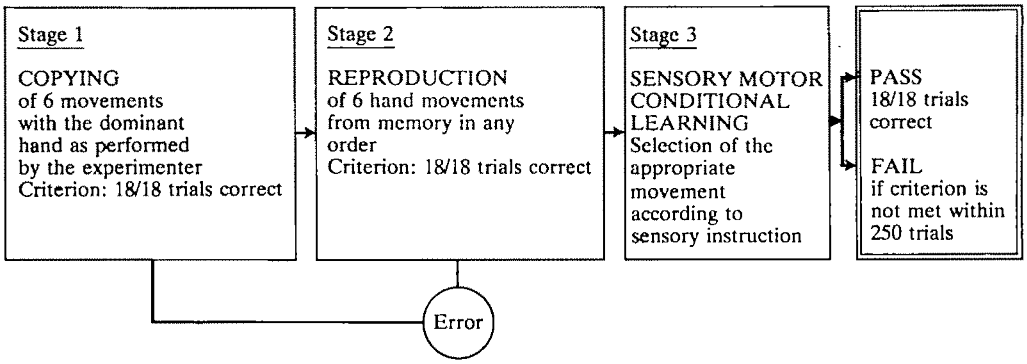

FIG. 1. Experimental arrangement for the sensory conditional motor tasks. At the beginning of the testing session, the subject was shown 6 hand movements, and the task was to copy the movements with the right hand (Stage 1). Thereafter, the subject was required to perform the movements from memory in any order (Stage 2). Finally, each of the 6 sensory stimuli had to be associated with one and only one of the hand movements which had been previously rehearsed (Stage 3).

was presented. The order of stimulus presentation was pseudorandom, with the restriction that all 6 stimuli would be presented once in every set of 6 trials and that no stimulus would be repeated on 2 consecutive trials. After each response the patient was informed whether he had performed the correct movement or not. A rerun correction procedure was used: if the subject made an incorrect response the trial was repeated until he succeeded. The criterion was 18 correct responses on 18 consecutive trials. Testing continued until the patient had learned the task or up to a maximum of 250 trials.

Experiment 2: sensory conditional spatial tasks (nonmotor selection)

The experimental arrangement is illustrated in fig. 2. The experimenter and the patient were seated at a table facing each other. On the table in front of the patient there was a board (40 cm×30 cm) with 6 black circles ($r = 1.9$ cm) placed in an irregular array. The patient was instructed that each circle was associated with 1 of 6 sensory stimuli, and that his task was to learn which spatial position was the correct one for each sensory stimulus. The patient responded by pointing to the appropriate circle associated with a given sensory stimulus. He was thus required to perform the same pointing movement to different locations in space.

The stimuli were the same as used in the sensory motor experiment described before presented in three sensory modalities: visual, auditory and tactile conditional learning. Within each modality on every trial, 1 of the 6 stimuli was presented in a pseudorandom order with the restriction that all 6 stimuli would be presented once in every set of 6 trials and that none of the stimuli would be repeated on 2 consecutive trials. After each response the patient was informed whether he chose the correct spatial position or not. If the subject made an incorrect response the trial was repeated until he succeeded (rerun correction procedure). The subjects were trained until they reached a performance level of 100% on 18 consecutive trials up to a maximum of 250 trials.

Computerized tomography

A complete set of 3 mm CT images was made for the upper 6 cm of the cranium of each patient with damage to the premotor or primary motor areas. CT scans were taken parallel to the glabella-inion line, determined in a lateral skull radiograph. The intercommissural line through the anterior commissure and the posterior commissure (CA-CP) was shown by Fox *et al.* (1985) to be orientated parallel to the glabella-inion line. In order to define the exact anatomical localization and dimension of the cerebral lesions as evident in CT images, the lesions were plotted onto the lateral diagram of a normalized brain (Talairach *et al.*, 1967). In this diagram the intercommissural line (CA-CP), the vertical lines on the anterior commissure (VCA) and on the posterior commissure (VCP), the vertical line between the CA-CP and the vertex (Z),

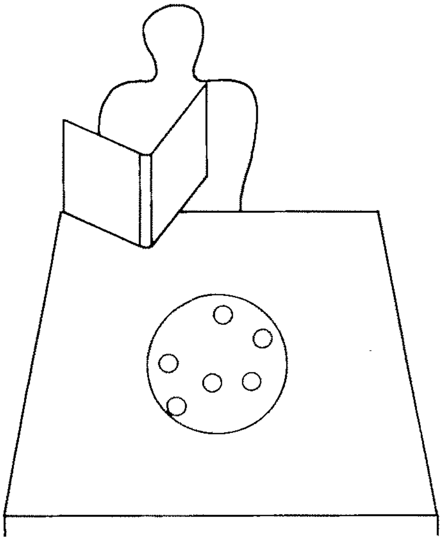

FIG. 2. Experimental arrangement for the sensory conditional spatial tasks. In front of the subject there was a board with 6 black circles placed in an irregular array. The subject was instructed that each circle was associated with 1 of the 6 sensory stimuli. The task was to learn which spatial position was the correct one for each sensory stimulus.

and the central sulcus were depicted. In all diagrams the precentral sulcus was delineated. In addition, the cerebral lesions were outlined in diagrams of horizontal brain sections orientated in parallel to the CA-CP. These diagrams were elaborated from the atlas by Talairach *et al.* (1967). In these diagrams the precentral, central and postcentral sulci and the frontal plane of the z axis are presented. From these graphic illustrations the observed brain lesions in the patients were determined in a three dimensional system of defined coordinates (fig. 3).

CASE REPORTS

Left-sided lesions

Case 1 (C.B.), female aged 76 yrs

Brain infarct; SMA, premotor and precentral. *Neurological assessment.* Distally accentuated weakness of right leg, proximal weakness of right arm. Walked with slight limp and climbed staircase normally. Muscle tone, grip strength and tendon reflexes normal. *Neuropsychological findings.* WAIS IQ 98. Motor dysgraphia with right hand in the absence of orthographic disturbances, agrammatism, and neologisms. Results on Reitan Indiana Aphasia Screening Test normal; below average on tests for cognitive flexibility (e.g., Trail Making, Part B). Mildly impaired on memory and attention tasks, but no indications of neglect.

Case 2 (R.P.), male aged 61 yrs

Brain infarct; premotor and SMA. *Neurological assessment.* Tone, grip strength and tendon reflexes normal. Minor disturbance of skilled hand movements on the right. Alternating movements normal. *Neuropsychological findings.* WAIS IQ 88. Initially 4 transient speech arrests. Leg fatigability and dysgraphia since childhood. Not impaired on memory and attention tasks.

Case 3 (W.K.), male aged 71 yrs

Brain infarct with carotid artery stenosis; medial premotor. *Neurological assessment.* Initially brachiofacial hemiparesis and motor aphasia resolving rapidly into mild residual clumsiness of right hand and minor dysarthria. Tendon reflexes and tone normal. Grip strength within normal range on both sides. Alternating

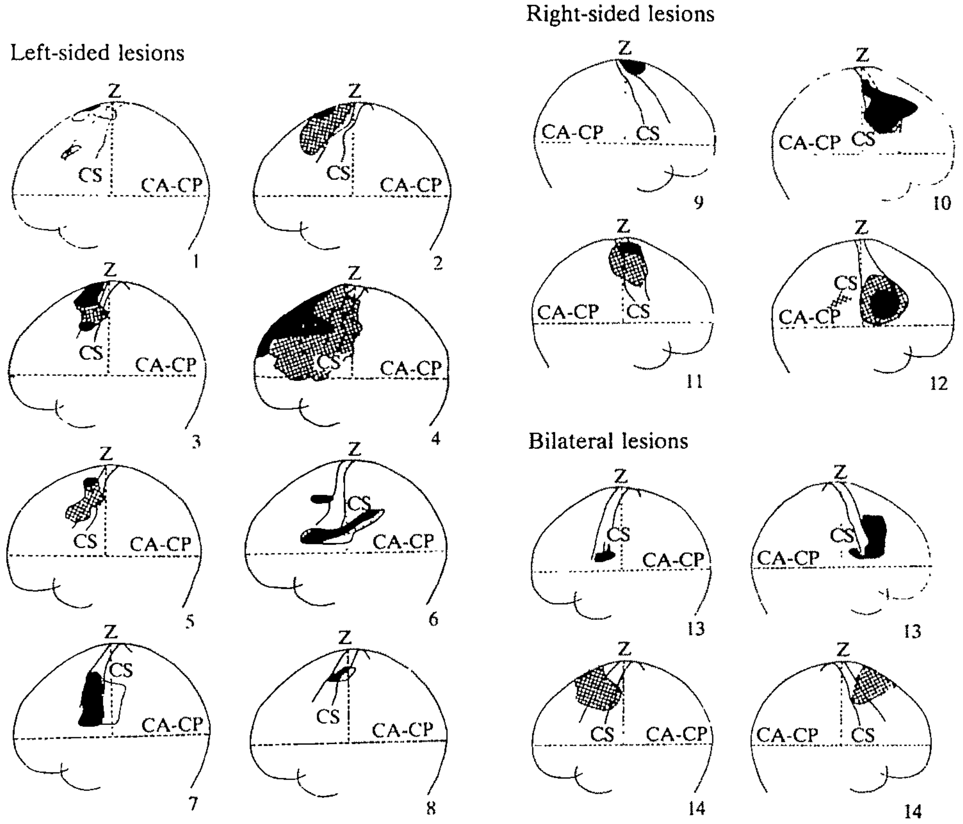

Fig. 3. Brain lesions as outlined on the lateral aspect of a normalized brain. CA-CP = intercommissural line; CS = central sulcus; Z = vertex. The cortical extent of the lesions is shown black, the subcortical extent by dotted areas. Case numbers are given below each diagram. For further explanation, *see* text.

movements unimpaired forwards, disturbed backwards. *Neuropsychological findings*. WAIS IQ 98. Motor dysgraphia with right hand in the absence of orthographic disturbances, agrammatism and neologisms. Results on Reitan Indiana Aphasia Screening Test normal; below average on tests for cognitive flexibility (e.g., Trail Making, Part B). Mildly impaired on memory and attention tasks, but no indications of neglect.

Case 4 (W.G.), female aged 75 yrs

Meningioma; lateral premotor, SMA and prefrontal; *Neurological assessment*. No proximal paresis. Disturbance in the performance of alternating movements of the arms or legs during forward and backward rotation. Tone and tendon reflexes slightly increased on right side. *Neuropsychological findings*. WAIS IQ 109. Normal results on Reitan Indiana Aphasia Screening Test. No impairment on memory and attention tests. Mildly impaired on Trail Making, Part B, but within normal range on Trail Making, Part A.

Case 5 (G.K.); male aged 64 yrs

Astrocytoma, grade III (operated); medial premotor. *Neurological assessment*. Proximal weakness of the right arm without any distal impairment of arm function. Tone and tendon reflexes normal. Grip strength within normal range on both sides. Windmill and cycling movements deranged in both directions.

Neuropsychological findings. Full-scale WAIS IQ 108. Mild nonfluent motor aphasia, naming deficits and dyscalculia. Impaired on Reitan Indiana Aphasia Screening Test. Severe motor dysgraphia with right hand. Mild impairment on memory and attention tasks without neglect.

Case 6 (J.A.), female aged 71 yrs

Brain infarct; lateral premotor, Broca's area and upper bank of the sylvian fissure. *Neurological assessment*. Initially slight hemiparesis and motor aphasia of sudden onset regressing to dysarthria and residual motor dysgraphia over 2 days. From second day normal grip strength; tone and tendon reflexes equal on both sides; normal facial movements. Alternating movements normal. *Neuropsychological findings*. WAIS IQ 120. Aachen's Aphasia Test (AAT) and Reitan Indiana Aphasia Screening Test revealed a mild impairment in the repetition of phonemic complex word configurations. Writing was difficult, but clearly legible without orthographic disturbances. Comprehension was excellent, including the understanding of complex relational sentences. Speech was fully grammatical without paraphasias and naming deficits. Not impaired on memory or attention tasks.

Case 7 (G.S.), male aged 59 yrs

Brain infarct; precentral, Broca's area. *Neurological assessment*. Initially complete motor aphasia, hemiparesis and hemihypaesthesia on right side, resolving into disturbance of skilled hand movements and dysarthria. Grip strength reduced in right hand; tone and tendon reflexes slightly increased on right. Plantar responses flexor. Position sense and stereognosis impaired in right hand. Tactile exploratory finger movements clumsy but not apraxic. Alternating movements normal. *Neuropsychological findings*. WAIS IQ 107. Not impaired on memory and attention tests, but below average on tests for cognitive flexibility (e.g., Trail Making, Part B). Impaired on Reitan Indiana Aphasia Screening Test.

Case 8 (V.H.), male aged 62 yrs

Brain infarct; precentral hand area. *Neurological assessment*. Monoparesis of right hand, initially complete, slowly improving over months. Initial transient hypaesthesia of forearm, not hand. Tone and tendon reflexes slightly increased in right arm. Precise force control and normal manual tactual exploration after partial recovery in spite of residual weakness. At this stage the patient could hold a fresh egg between the thumb and the other fingers without dropping or squeezing it. Manual skills improved, so that this skilled dentist regained the capacity to use his hand for drilling and manipulating, although with early fatigue and residual grip force reduced to only two-thirds of left hand. Capacity for rapid alternating independent finger movements never regained. Alternating movements normal. *Neuropsychological findings*. WAIS IQ 132. Writing and performance on dexterity tests ('Schuhfried's Motorische Leistungsserie') almost normal. Not impaired on memory and attention tests (e.g., SKT, Wechsler Visual Memory Scale, Trail Making, Part A).

Right-sided lesions

Case 9 (H.B.), male aged 49 yrs

Cerebral contusion; SMA. *Neurological assessment*. TR, tone and grip force normal, minor slowing of alternating finger movements and tapping; flawless performance of independent finger movements, but unable to copy finger postures or assume such postures on verbal command. Windmill movements backwards with left arm impossible. *Neuropsychological findings*. WAIS IQ was 125. Cognitive flexibility within normal range. Not impaired on formal memory and attention tests, but complained of difficulty in concentrating.

Case 10 (F.M.), male aged 40 yrs

Grade II astrocytoma (operated); precentral and most lateral part of PMC. *Neurological assessment*. Completely normal. *Neuropsychological findings*. WAIS IQ 106. Mild impairment on memory and attention test battery (SKT).

Case 11 (I.L.), female aged 52 yrs

Glioma (stereotactic biopsy); precentral and medial premotor. *Neurological assessment.* Proximal weakness on the left side, manual skills normal. Grip strength equal on both sides. Tendon reflexes increased on left, tone normal. Windmill and cycling movements unimpaired forwards, impossible backwards. Plantar responses flexor. Two months after testing develop a pyramidal syndrome and cognitive dysfunction. *Neuropsychological findings.* WAIS IQ 97. Not impaired on memory and attention tests of SKT battery and Trail Making, Part A. But impairment on visuoconstructive memory test (Wechsler Visual Memory Scale) and on tests for cognitive flexibility (e.g., Trail Making, Part B). Within normal limits on Seashore rhythm discrimination task, but impaired in rhythm production with the contralateral hand.

Case 12 (E.S.), female aged 64 yrs

Oligodendroglioma; lateral premotor and precentral. *Neurological assessment.* Very mild weakness of left arm and face. Manual skills normal. Tendon reflexes increased on left, tone normal. Windmill and cycling movements unimpaired forwards, impossible backwards. Optokinetic nystagmus abolished to the left. *Neuropsychological findings.* WAIS IQ 97. Impaired in Luria's test battery. Memory and attention tests within normal range. Impaired in producing a simple melody with the xylophone subtest of the TŪLUC.

Bilateral lesions

Case 13 (H.D.), female aged 63 yrs

Brain infarct; right premotor and left upper bank of sylvian fissure. *Neurological assessment.* Right hand clumsy. Limb-kinetic apraxia of both arms. No windmill or cycling movements possible. Buccofacial apraxia. *Neuropyschological findings.* WAIS IQ 90. Initially complete motor aphasia, regressing to dysarthria and dysprosody. Aachen's Aphasia Test and Reitan Indiana Aphasia Screening Test showed impairment in repetition of spoken language, naming difficulties and dyscalculia. Comprehension of complex relational sentences severely disturbed, but performance in Token Test within normal range. Severe dysgraphia with literal disintegration with both hands. Severe impairment on memory and attention test battery (SKT) and on Trail Making, Part A; excluded from associative learning tasks. Severely impaired in sustaining correct alternating response between numbers and letters (Trail Making, Part B).

Case 14 (B.R.), female aged 60 yrs

Metastatic tumour; extensive subcortical white matter lesion below both premotor fields, invading prefrontal cortex. *Neurological assessment.* Severe slowing of movements, in particular for proximal movements on right side. Windmill and cycling movements impossible. Unsteady dysbasic gait. Grip strength, tone and tendon reflexes normal. *Neuropsychological findings.* WAIS IQ 90. Severe dysgraphia. No neglect, but excluded from present associative learning paradigms because of severe global impairment in memory and attention tasks. Unable to produce simple rhythms with left or right hand.

RESULTS

Nature of the motor disturbances as revealed by clinical examination

Precentral lesions. The characteristic deficit was weakness with only a minor increase of muscle tone and in the tendon reflexes. After partial recovery from the paresis, a disturbance of alternating finger movements remained as a persistent deficit and was associated with a disturbance of manual skills that was proportional to the impairment in the selective control of independent finger movements. The patients with almost pure left-sided M1 lesions (Cases 7, 8) showed only small precentral hypodense areas due to infarcts with initially complete paresis of the arm. But both patients recovered so well (Freund, 1987) that they could perform the required sensory conditional motor tasks of the present study with the affected arm without difficulty. Force and position control was surprisingly precise. As soon as the fingers could perform flexion synergies permitting slow alternating movements of the fingers against the thumb, the patients were able to recognize haptic objects when blindfolded. Movements were slower than normal, so that rapid alternating manual activities such as writing were disturbed. The individual writing pattern was re-established later in the course of recovery.

Premotor lesions. In patients with more *medial* lesions the characteristic deficit was the same as described elsewhere (Freund and Hummelsheim, 1985). Patients with lesions of the *lateral* premotor area, sometimes involving Broca's area showed, in addition to motor aphasia or dysarthria, a dysgraphia which was always dyspraxic and not aphasic. This dysgraphia could not be attributed to the impairment of hand function from damage to the M1.

Lesions of the supplementary motor area. Only 1 patient (Case 9) had a lesion due to a brain contusion that was restricted to the supplementary motor area. The major deficit, differing from that seen in the other patients, was the obvious difficulty he had in bringing his fingers into certain positions either on imitation or on verbal command. This deficit was described by Luria (1966).

Relationship between the location of the lesions and neurological deficits

As in the cases reported by Freund and Hummelsheim (1985) we also included in this series those patients in whom the lesion extended into the precentral gyrus. The anterior part of this gyrus represents area 6 and therefore is part of the PMC. It is, however, impossible to delineate the border between areas 6 and 4. Our present policy was therefore to distinguish those cases with preferential involvement of PMC and/or SMA on the one hand and the primary motor area (M1) on the other. This distinction correlated well with the clinical picture.

This conservative attitude is supported by the poor correlation between the extent of hypodense areas as revealed by CT and the disturbance of function. This is best illustrated by Case 10 who had an astrocytoma infiltrating large parts of the precentral gyrus. That patient was completely normal on examination, including special tests for hand function. It is well known that such patients become paretic after operation. Tumour infiltration therefore seems to be compatible with the preservation of function.

Sensory conditional learning tasks

Fig. 4 gives the mean number of errors for the experimental groups with preferential damage to the PMC or M1 as compared with the healthy controls and subjects with parietal lesions who served as additional controls. The results are based on the total number of errors made by the subjects to criterion level (18/18 correct responses) up to a maximum of 250 trials. An error was defined as an inappropriate movement choice on the sensory conditional motor tasks, or the selection of a wrong spatial position, that is, pointing to a circle which was *not* associated with the presented sensory stimulus

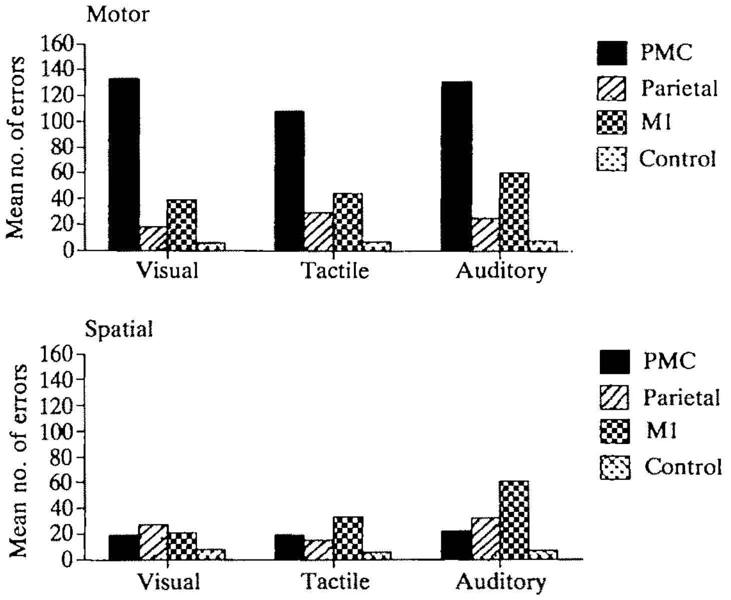

FIG. 4. Mean number of errors made by the experimental groups with preferential damage to the premotor (PMC) or primary motor (M1) areas as compared with patients with parietal lesions and healthy control subjects on the sensory conditional motor (*top*) and spatial conditional (*below*) tasks. The results are based on the total number of errors made by the subjects to criterion level (18/18 correct responses) up to a maximum of 250 trials.

on the conditional spatial tasks. The patients with lesions involving PMC and/or SMA made significantly more errors than the controls or the patients with parietal or M1 lesions (Mann-Whitney U test, $P < 0.01$) when they had to select between movements according to visual, tactile and auditory instructions. By contrast, there was no significant difference between the number of errors made by the patients with parietal lesions or damage with preferential involvement of M1 and the controls. Patients with lesions of the PMC or SMA had difficulties when they had to recall a movement from memory on the basis of a sensory cue. This deficit occurred when visual, tactile or auditory cues were used. By contrast, patients with parietal lobe damage or lesions with preferential involvement of M1 did not show a significant discrepancy in performing sensory conditional motor and spatial tasks.

Next, the mean number of errors made by the various groups on the sensory conditional motor and spatial tasks was calculated separately for left and right-sided cortical lesions (fig. 5). The results indicate that severe deficits in conditional motor learning occurred in patients with damage to the premotor areas both contralateral and ipsilateral to the lesions; all patients were right-handed and only their dominant hand was tested irrespective of the side of the lesion. Thus in patients with right-sided brain damage an ipsilateral hand deficit was scored.

Fig. 6 gives the number of errors made by individual subjects on the sensory conditional motor and sensory conditional spatial tasks. The data show that a deficit in conditional motor learning occurred regardless of a medial or a more lateral anatomical location.

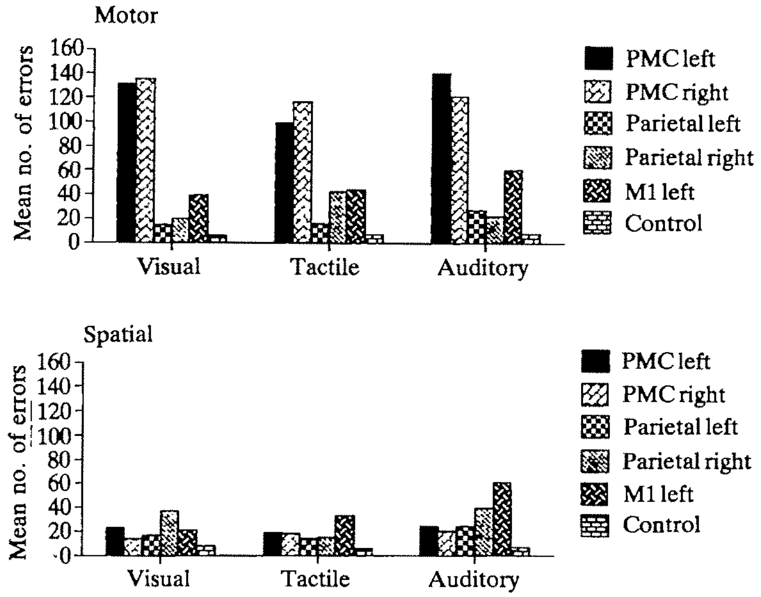

FIG. 5. Same arrangement of data as in fig. 4, but in this fig. the mean number of errors made by the various groups on the sensory conditional motor (*top*) and spatial (*below*) tasks (criterion: 18/18 correct responses) was calculated separately for left and right-sided cortical lesions.

They also show that patients with only small PMC lesions (Cases 1, 5) were less severely impaired on the sensory conditional motor tasks than those patients with predominant damage to the PMC and/or SMA.

A separate analysis was performed on the number of trials needed by the various groups to meet criterion (18 correct responses on 18 consecutive trials). Training on these tasks continued until the subject had met criterion up to a maximum of 250 trials. If the subject made an error, the trial was repeated until he succeeded (rerun correction procedure). It was found that the number of trials needed to reach criterion by our groups with damage to the PMC and/or SMA differed significantly (Mann-Whitney U test, $P < 0.01$) from the scores obtained by the other subjects on the three sensory conditional motor tasks (fig. 7). Six of our patients with lesions involving the PMC failed to reach criterion within the limits of testing (250 trials) on the visual conditional motor tasks. The tactile conditional motor task was not passed by 5 and the auditory conditional motor task by 7 of our patients with premotor damage.

The difficulties in selecting the appropriate movement according to a sensory instruction is not due to a failure in remembering the 6 arm movements. All patients were able to produce the complete set of 6 hand movements 3 times in a row within a small number of acquisition trials; the mean number of trials needed by the various groups during free recall of the 6 arm movements was as follows (criterion: 18/18 correct): PMC lat. = 12; PMC med. = 12; PMC+SMA = 15; SMA = 12 trials.

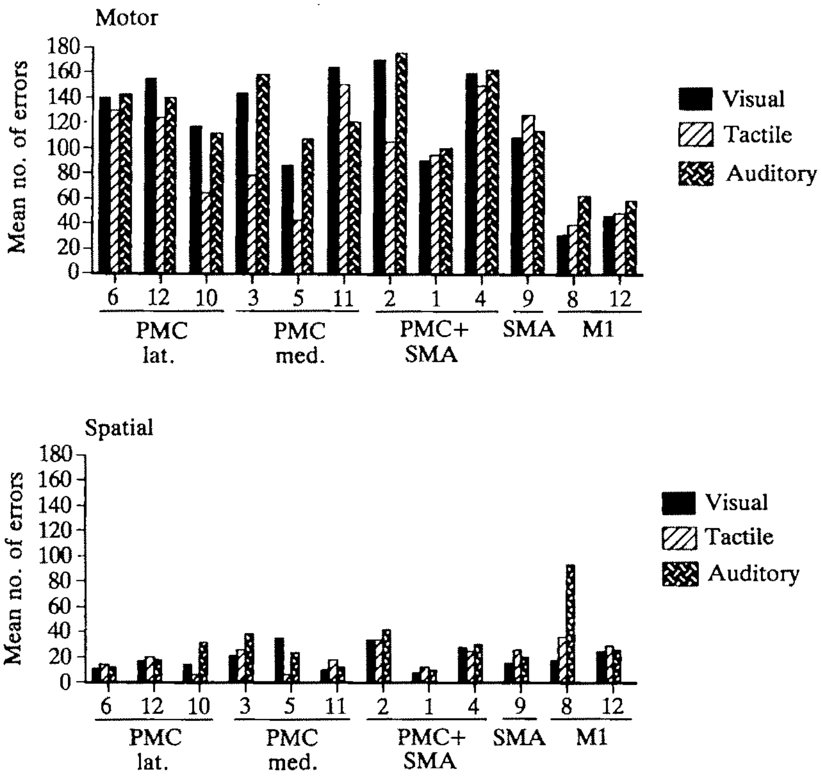

FIG. 6. Number of errors made by individual patients with preferential involvement of the premotor (PMC) or primary motor (M1) cortex on the sensory conditional association tasks. Subjects with lesions located preferentially in the lateral (lat), medial (med.) or supplementary (SMA) motor area were grouped together.

DISCUSSION

The results of this investigation show that lesions of the PMC cause impairment in the learning of conditional tasks requiring the production of different movements in response to visual, tactile or auditory stimuli, but not in learning of conditional tasks requiring responses to 6 spatial locations.

Control experiments indicate that the failure of the patients on the conditional motor tasks does not result from a difficulty in making individual movements or in discriminating between the sensory stimuli. These patients were able to reproduce the 6 movements from memory, and they mastered successive discriminations within the visual, tactile and auditory modalities. Furthermore, they can interpret and make use of sensory cues: these patients can perform sensory conditional tasks correctly when they have to choose between different spatial locations. On this task the cue must prompt the patient to retrieve a particular spatial position from memory rather than a movement in a particular direction.

The present findings are consistent with the results from nonhuman primate research which suggest that the PMC plays a role in visual guidance of movements (e.g.,Godschalk

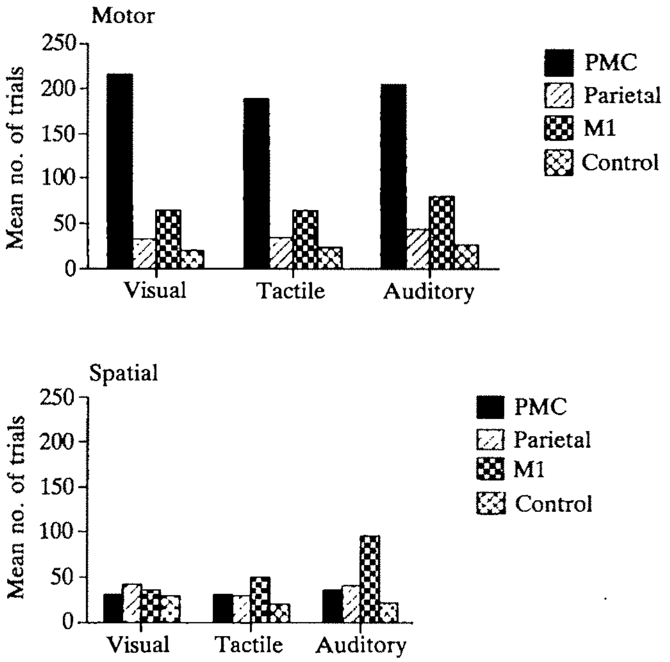

FIG. 7. Mean number of trials needed by the various groups to meet criterion on the sensory conditional motor (*top*) and spatial (*below*) tasks. The results of the patients with left or right-sided cortical lesions were pooled together. PMC = premotor cortex; M1 = primary motor cortex.

et al., 1981; Rizzolatti *et al.*, 1981; Halsband and Passingham, 1982, 1985; Petrides, 1985*a*). Halsband and Passingham (1982, 1985) and Halsband (1987) have shown that monkeys with PMC ablations were impaired at relearning a task in which they had to select one of two movements as instructed by a visual cue. It was found that the same monkeys were able to learn a nonmotor visual conditional task in which the visual cues specified which object should be chosen. Similarly, Passingham (1985) trained monkeys to pull or to turn a handle as instructed by the colour of a background cue, and again the monkeys with premotor lesions were impaired. It was concluded that monkeys with PMC lesions were impaired only when they must recall a movement from memory on the basis of a visual cue.

A crucial factor seems to be that in all these experiments it was visual cues from the *context* that must prompt recall of specific actions. Passingham (1985) has shown that monkeys with PMC lesions can recall actions if they are prompted by the identity of the object that they must manipulate. This interpretation might also be applied to the present results: clinical observations of patients with PMC lesions do not reveal any deficits in selecting the appropriate action during their daily ward activities. But the same patients have serious difficulties in test situations where an arbitrary sensory cue is used for directing the movement.

The experiments described here make a further point, that the PMC is not confined to the selection of action according to visual cues. Instead the experiments argue for a role of PMC and SMA in directing movements on the basis of sensory stimuli from different modalities, that is, visual, auditory and proprioceptive cues. There is evidence from electrophysiology with which to support this claim (Rizzolatti *et al.*, 1981; Weinrich and Wise, 1982; Tanji, 1985; Kurata and Tanji, 1986). The findings by Kurata and Tanji indicate that auditory and somatosensory inputs are no less potent than visual stimuli in activating PMC neurons when these stimuli are used as a movement trigger.

The data from electrophysiology are in agreement with anatomical studies which indicate that cortical association areas direct their influence on motor cortex via the PMC and SMA (Pandya and Kuypers, 1969; Chavis and Pandya, 1976; Godschalk *et al.*, 1984). Both the dorsal PMC and SMA can receive somatic and visual information directly from the parietal cortex, in particular areas 5 and 7 (Jones *et al.*, 1978; Bowker and Coulter, 1981; Petrides and Pandya, 1984), but also via the cerebellar-thalamic route (Glickstein *et al.*, 1985).

The present data do not support the existence of two cortical systems for directing movements, whereby the SMA is specialized for the direction of movement on the basis of proprioceptive cues and PMC for the direction of action according to visual instructions (Passingham, 1987). The performance of our patients with damage to the PMC and the SMA did not differ from those without SMA involvement. The findings on differences between the PMC and SMA in human subjects must, however, be interpreted with great caution since all but 1 patient with a lesion in the SMA also showed some damage in the PMC.

The results of the present study make one further point: patients with posterior lesions or primary motor lesions of a size comparable to the experimental group do not show impairment in the sensory conditional tasks. These patients had no difficulties in associating different arm movements or different spatial locations with sensory cues, and there was no difference in the number of trials needed to meet criterion or in the number of errors made on the sensory conditional tasks after damage to the parietal cortex or MI lesions. The fact that our control subjects as well as our patients with parietal or M1 lesions had no more difficulties in mastering the conditional *spatial* tasks as compared with the *motor* tasks makes it unlikely that the second task was much more difficult. There is, however, a crucial difference between the two tasks: in the spatial task the spatial locations are in front of the patient, and it is easy to associate a cue with something physically present. In the conditional motor task the association is with an event (the arm movements) that is not present, but stored in memory. However, the findings that our premotor patients had no difficulty in learning to associate pairs of words (Wechsler Memory Scale) show that these patients did not have a generalized impairment in associating events that are not physically present. Instead, they point to a more specific role of premotor cortex in conditional motor learning. What further becomes evident from our study is the significance of the PMC for bilateral movement control. Since the deficits in conditional motor learning have been observed both contralateral and ipsilateral to the lesions, sensory and conditional motor learning seems to require the integrity of both PMCs. On the paradigms tested here, no clear differences were seen between left and right-sided lesions. However, the findings by Verfaellie and Heilman (1987) suggest that in patients with damage that includes the SMA, both hemispheres may contribute asymmetrically to the processes of response preparation and inhibition. They concluded that a lesion of the left SMA may not as readily interfere with response preparation and inhibition as does a lesion of the right SMA. Only 2 subjects were studied, and clearly more data are needed before firm conclusions can be drawn.

The results of the present study are compatible with the hypothesis that the premotor areas are bilaterally organized parts of the frontal agranular motor field that are relevant for the sensory cueing of movement and for motor learning. Several questions remain unanswered, and further studies are needed to provide clues as to whether the kinetic engrams emerging in the course of motor learning are stored in the same neuronal repertoire where they are formed. We have examined whether patients with PMC lesions can assign a colour or some other arbitrary sensory stimulus to movements executed by the experimenter. In such a task the patient would be compelled to remember the different movements but not to evoke them. Our preliminary findings (Halsband and Freund, unpublished) indicate that patients with premotor lesions are impaired on this task, but they perform significantly better on this version as compared with the sensory conditional motor tasks reported in the present study.

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KONZO, AN EPIDEMIC UPPER MOTOR NEURON DISEASE STUDIED IN TANZANIA

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SUMMARY

An epidemic of spastic paraparesis was studied in a drought-affected rural area of Tarime district in northern Tanzania. The uniform clinical findings in 39 cases, aged 4–46 yrs, indicated abrupt symmetric isolated and permanent but not progressive damage to the upper motor neurons. Due to the failure of other food crops, the diet at onset consisted almost exclusively of bitter cassava roots, a drought-tolerant starchy root crop widely cultivated in Africa. The drought increased the natural occurrence of cyanogenic glucosides in the cassava roots, and the processing procedure normally applied in order to remove cyanide before consumption was shortened because of food shortage. The resulting high dietary cyanide exposure was confirmed by very high serum levels of thiocyanate, the detoxification product of cyanide. Tests for HTLV-1 antibodies were negative and no other findings supported an infectious aetiology. The clinical findings and the associations with cassava toxicity are almost identical to those reported from outbreaks of spastic paraparesis in Mozambique and in Zaire, where this disease was first reported under the name 'konzo'. We thus conclude that konzo constitutes a distinct upper motor neuron disease entity, probably caused by a toxic effect from insufficiently processed cassava under adverse dietary circumstances.

INTRODUCTION

Outbreaks of permanent spastic paraparesis of acute onset have been reported during dry seasons in Bandundu Region in Zaire (Trolli, 1938; Lucasse, 1952; Anonymous, 1982) and as an extensive epidemic in a drought-affected area in Mozambique (Ministry of Health, Mozambique, 1984*a*). In both countries, children and young adults from poor peasant families were affected, and the clinical findings were identical (Carton *et al.*, 1986). This form of spastic paraparesis differs but also shows similarities with other forms of myeloneuropathies reported from populations in tropical countries (Cruickshank, 1976; Román *et al.*, 1985). Most similar is lathyrism, an acute form of spastic paraparesis caused by consumption of large quantities of the chickling pea (*Lathyrus sativus*), a drought-resistant crop consumed in parts of Ethiopia, India and Bangladesh (Ludolph *et al.*, 1987). A neuroexcitatory amino acid in the pea has been shown in an animal model as the most probable aetiological factor (Spencer *et al.*, 1986). The recent findings of antibodies to HLTV-I in a similar form of spastic paraparesis with slow onset in late adulthood indicate an aetiological role for this virus in the disease

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named tropical spastic paraparesis or HTLV-I-associated myelopathy (Anonymous, 1988).

The outbreak of spastic paraparesis in Mozambique was associated with high cyanide and low sulphur intake from a diet dominated by insufficiently processed toxic cassava roots and lacking protein-rich supplementary foods to supply the sulphur needed for cyanide detoxification (Cliff *et al.*, 1985; Rosling, 1986). Due to high yields and good drought tolerance cassava roots are an important staple crop in many parts of Africa, but the roots contain cyanogenic glucosides that must be removed by careful processing before consumption (Cock, 1982). The outbreaks of spastic paraparesis in both Mozambique and Zaire occurred in two of the most highly cassava-dominated areas in Africa and an aetiological role for cassava toxicity was suggested as early as in the first report by Trolli (1938). An infectious aetiology has also been proposed (Carton *et al.*, 1986)

The present study reports clinical, epidemiological and laboratory findings from an outbreak of cases of spastic paraparesis in a drought-affected rural area of Tarime district in Tanzania that are almost identical to those reported from Mozambique and Zaire. The results indicate that this form of upper motor neuron damage is a distinct disease entity, aetiologically related to cassava toxicity and best named 'konzo', the local name used in the area of Zaire where it was first reported.

SUBJECTS AND METHODS

Study area

Tarime district is situated in Mara region in northern Tanzania and borders Kenya and Lake Victoria (fig. 1). The population is 260,000, with a density of 67 inhabitants per km^2, which is higher than average for rural Africa. The outbreak studied occurred in the dry west lowlands of the district that are mainly populated by the Luo tribe, living in large villages created during the villagization programme in the seventies. This lowland area has a limited agricultural suitability, the main staple crop being cassava, but maize and sorghum are also grown, and fish from the lake are eaten when available. Most families keep cattle and goats, but they are rarely eaten.

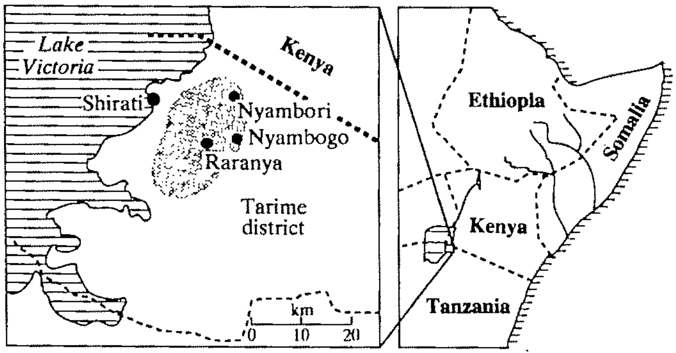

FIG. 1. The villages studied and the area from which cases of spastic paraparesis were reported in 1984–1985.

Subjects

The villages Raranya, Nyambori and Nyambogo were chosen for this study because of their location in the middle of the area from which cases of paralysis were reported to Shirati Hospital from March 21 until the end of May 1985 (fig. 1). Village leaders and paramedical staff in charge of the village dispensaries screened each village for paralysed subjects, who were examined in their homes during three-day visits in May, June and July 1985 by the consultant neurologist for northern Tanzania (W.P.H.). The case histories were obtained through interviews in the local language by a medical assistant from the area and by a physician (G.B.) who has worked in the district for 20 yrs.

The criterion for inclusion was onset of difficulty in walking during the previous year due to paralysis of the legs in the absence of any other well defined neurological disease. Out of the about 50 cases presented for examination, 1 case of recent transverse myelopathy with sensory loss up to a defined level on the trunk as well as cases of poliomyelitis and cerebral palsy were excluded. A total number of 39 cases were thereafter included in the study, 20 in May, 6 in June and 13 in July. Fifteen of the 20 cases examined in May, all with onset in March to May, were selected for follow-up examination in June 1985 and March 1986 by the same physician.

Procedure

A brief general examination was followed by a detailed neurological examination. Visual acuity was tested by counting fingers at 1 m, visual fields by the confrontation method and pursuit eye movements to a hand in four positions. Pupillary reflexes, including consensual responses, were tested with a torch inside the dark huts. Fundoscopy was undertaken with a Keller ophthalmoscope, and hearing was tested with a watch. Power in the legs was graded according to the Medical Research Council (1976) scale. Superficial sensation was tested with cotton wool and pin prick, posterior column sensation by joint position sense and the plantar responses with the legs in an extended position.

Dietary information was obtained from village leaders as well as by observations and open question interviews during home visits to all affected families. The interviews covered agricultural practices, use of pesticides, cassava processing methods, wild plant consumption and food habits before and during the outbreak. Rainfall data were obtained from Shirati Hospital.

For laboratory investigation, 10 ml of blood was collected from each of the 39 cases identified at the time of the first examination. In May blood was also collected from 9 nonaffected family members. Serum was separated within hours and thereafter stored and transported frozen until the time of analysis. Presence of HTLV-I antibodies was tested with Biotech ELISA kit and western blot with disrupted virons produced by the HUT-102 cell line as antigen at Laboratoire d'Épidémiologie et Immunovirologie des Tumeurs, Faculté de Medicine Alexis Carell, Lyon, France. Serum thiocyanate was determined as an indicator of cyanide exposure by a colorimetric method after interfering compounds had been eliminated by ion-exchange chromatography on resin Amberlyst A-21 (Lundqvist *et al.*, 1979, 1983) at the Department of Clinical Chemistry, Linköping University, Sweden. Total protein was estimated by the biuret method, and schistosome serology (indirect fluorescent antibody technique) and the VDRL tested at the Kilimanjaro Christian Medical Centre, Moshi, Tanzania.

RESULTS

Epidemiological findings

A total of 39 cases, 30 males and 9 females aged 4–46 yrs, with a first attack or relapse attack of symmetric spastic paraparesis between September 1984 and June 1985 were identified in the 3 villages studied (Table 1, 2). A second attack during the previous year was reported in 3 out of 39 cases, and the distribution in time of the resulting 42 onsets is shown in fig. 3. Eleven of the cases studied gave a history of a previous

TABLE 1. NEW CASES OF KONZO IDENTIFIED*

Village	*Population*	*No. of cases*	*Cases per 1,000 inhabitants*
Raranya	2,600	7	2.7
Nyambori	3,900	14	3.6
Nyambogo	3,700	18	4.9
Total	10,200	39	3.8

* September 1984 to June 1985.

TABLE 2. AGE AND SEX DISTRIBUTION OF THE CASES

	Age (yrs)							
	0–4	*5–9*	*10–14*	*15–19*	*20–24*	*25–29*	*30–49*	*Total*
Male	2	6	12	6	0	2	2	30
Female	0	1	2	3	1	1	1	9
Total	2	7	14	9	1	3	3	39

attack of the same disease in 1973 or between 1980 and 1984. Three old cases with the same type of spastic paraparesis but with no new attack in the previous year were not included. Most cases were first examined within 3 months of the onset (range 10 days–8 months). Many families had more than one member affected, and 19 cases came from only 6 families, 5 from 1 single family.

More than 10 similar lowland villages in the area marked in fig. 1 were reported to have had similar outbreaks during February to May 1985. The total number of cases affected by spastic paraparesis during this outbreak was therefore far higher than 39. In spite of inquiries with local authorities and health staff, no case was reported in the fishing villages along the coast of Lake Victoria or in the semiurban district capital and adjacent, more fertile highlands in the eastern part of the district (fig. 1).

Neurological findings

The course of the disease was similar in all 39 cases identified: abrupt in onset with initial difficulty in walking, progressing to paraparesis over the next 2–3 days (range 1–7 days). Initial symptoms were described as heaviness of the legs, difficulty in walking, trembling of the legs, a tendency to fall on walking or an inability to stand. Typically, a previously healthy individual either woke up in the morning with these symptoms or developed them during or shortly after a long walk. There was no history of fever, diarrhoea or other preceding illness, but during the first few days all patients complained of generalized weakness. A typical history obtained from 36 out of 39 patients was difficulty or inability to rise from the supine to the sitting position during the first day of the disease. This was accompanied in 12 cases by pain in the lumbar region radiating down to the legs and in 10 cases by numbness in the legs. Fifteen cases complained of difficulty in speaking and 8 of difficulty with vision.

The striking physical finding in all cases was a symmetric spastic paraparesis varying in degree from hyperreflexia associated with increased tone to paralysis of the legs, as shown in Table 3. The plantar responses were extensor in 85%. Power was reduced in the legs in 32 of 39 cases. The loss of power particularly affected the hip and knee flexors as well as the plantar flexors of the feet as shown by the testing of separate muscle groups (Table 4). A marked increase in muscle tone in the legs resulted in spasm in flexion, particularly affecting the ankle joints and in severe cases leading to contractures (fig. 2). Thoracolumbar kyphoscoliosis, noticeable on standing, was present in 15 of the 34 cases able to stand. In the upper limbs, weakness was mild, except for 2 of the most severe cases, and mainly affected the extensor muscle groups at the wrist and elbow.

There was no loss of sensation to light touch or pin prick, and joint position sense was normal in all cases. Two patients who had impaired rapid alternating movements and 1 with additional intention tremor had associated weakness of the upper limbs, making interpretation difficult. Nystagmus was absent in all cases, and Romberg's test negative in all cases able to stand without support. All 8 cases complaining of difficulty in seeing could count fingers at 1 m, but 6 had pale optic discs and 5 of these had a history of previous attacks of spastic paraparesis. The 15 cases who complained of difficulty in speaking gave a history of hoarseness, weakness and periodic absence of the voice which had cleared in all except 2 in whom a nasal voice was observed. Both had an impaired gag reflex. Pupillary reflexes were normal, no deafness was found and the jaw jerk was absent in all cases. On general examination tropical ulcers and signs of scabies were seen in some patients, but no signs of anaemia, visible goitre or gross malnutrition were found.

One month later, at the follow-up in June 1985, 14 of the 15 reexamined cases reported

TABLE 3. MAIN NEUROLOGICAL SIGNS IN 39 CASES

	No. of cases	*Frequency (%)*
Hyperreflexia in legs	39	100
Hypertonus in legs	36	92
Ankle clonus	35	90
Extensor plantar responses	33	85
Hyperreflexia in arms	22	56

TABLE 4. MUSCLE POWER IN THE LEGS IN 39 CASES

	*Muscle power grades**				
	1	*2*	*3*	*4*	*5*
Hip flexors	0	1	19	9	12
Knee flexors	0	2	21	9	7
Knee extensors	0	0	5	22	12
Ankle plantar flexors	0	2	21	9	7
Ankle dorsiflexors	0	1	8	21	9

* Graded according to Medical Research Council (1976) scale: 0 = no movement; 1 = trace of contraction; 2 = movement with gravity eliminated; 3 = movement against gravity; 4 = movement against resistance; 5 = normal power.

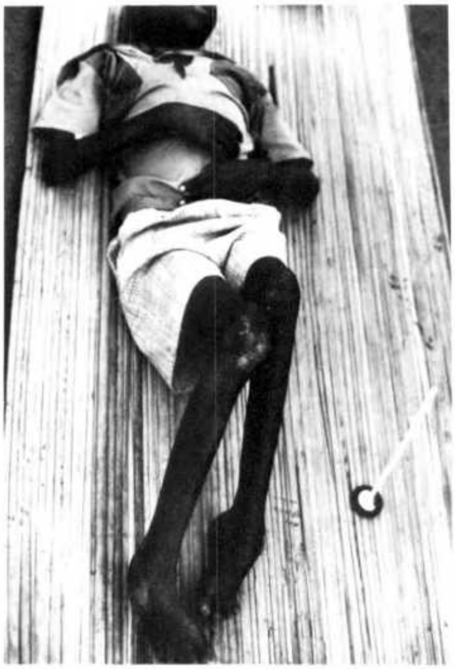

FIG. 2. A severe case of konzo with contractures in lower limbs.

some functional improvement, mainly in the trunk muscles and legs. Dysaesthesia had by then cleared in all affected cases, but 1 still complained of difficulty in seeing and 2 of difficulty in speech. The neurological signs were unchanged in all cases except for a definite decrease in muscle spasm at the ankle joint.

At the follow-up examination in March 1986, 10 months after the first examination, the neurological signs were still unaltered from the initial examination. All were left with an unchanged persistent spastic paraparesis in flexion characterized by a scissors gait, flexion at the hips and knees, valgus ankle deformity and plantar flexion of the feet with abduction of the forefoot and toes. Nine patients needed a stick to walk, 4 needed additional support to walk, and 1 was unable to stand even with support. Four of 15 complained of paraesthesiae in the feet, but again no loss of sensation was found, and 2 yrs later in May 1988 these 4 patients were asymptomatic with respect to sensory symptoms. The other symptoms and signs were unchanged in the 10 patients reexamined in May 1988, except for decreased pallor of optic discs in 2 previously affected cases.

Dietary history

A stiff porridge made from flour of processed cassava roots is the main staple food in the affected villages. The most commonly cultivated cassava varieties, called 'kigoma' and 'ndiaraye', are bitter in taste and were introduced in the villages around 1980 because of their high yield and good drought tolerance. Before consumption the toxic components are removed from these bitter roots by a locally used processing method. Roots are first peeled and crushed with a wooden mallet into pieces some centimetres in size which are piled together on a rock and covered with heavy stones for about 72 hours to squeeze the juice out and allow fermentation to take place. The covering stones and the outer greyish mould layer are thereafter removed; the pieces are further crushed by a wooden mallet, spread evenly over the rock and left to dry in the sun for a full day. Finally, the dry pieces are pounded into a flour, which is mixed with sorghum, millet or maize if available, before being mixed with boiling water for some minutes to make the thick staple porridge, 'ugali'. Cassava leaves, preferably from sweet varieties, and other green leaves are used to make a relish by prolonged boiling in water. The most important protein-rich supplementary foods are fish and milk. Beans, groundnuts and meat from the cattle and goats that are kept are rarely eaten.

The rainfall in 1984 was 540 mm, which was the lowest on record in Tarime district. The drought resulted in loss of maize and sorghum harvests during the weak rain period in March–May 1984. This was followed by a steep increase in cereal prices in the second quarter of 1985, and most families experienced food shortage until the following cereal harvest in May 1985, 2 months after the start of the following rain period in March 1985, as shown in fig. 3. However, in spite of drought, the bitter cassava varieties produced reasonable yields and, in the affected families as well as in many other households in the villages studied, the diet during the most severe food shortage period in February–May 1985 consisted almost exclusively of cassava porridge made from bitter roots. Because of the lack of food these roots were harvested earlier than usual, and processing was shortened. Fish were available in the local market during the food shortage period, but apparently it was rare in the diet of the affected families owing to the economic difficulties inflicted on these peasants by the drought. During the period of food shortage the only supplementary food regularly eaten in affected families was a relish of leaves from the bitter cassava varieties. The leaves were boiled for some hours, sometimes in repeated changes of water to eliminate toxic substances. In June 1985, after a normal rain period, the dietary situation improved, and the families had sorghum to mix with the cassava flour.

Affected families denied having consumed wild plants because of food shortage or having used any form of pesticide or toxic chemicals, nor was such use observed or reported by community leaders. No *Lathyrus sativa* was consumed, since this plant is unknown in the area.

Laboratory findings

The mean (± SEM) serum thiocyanate levels in 20 cases and in 9 nonaffected family members examined in May were 368 ± 30 and 303 ± 30 μmol/l, respectively. The thiocyanate levels in the 6 and 13 cases examined in June and July were 256 ± 56 and 184 ± 39 μmol/l, respectively (fig. 3).

No antibodies to HTLV-I were found in the 39 cases or in the 9 nonaffected family members, nor was the VDRL positive in any of these subjects. Schistosoma serology

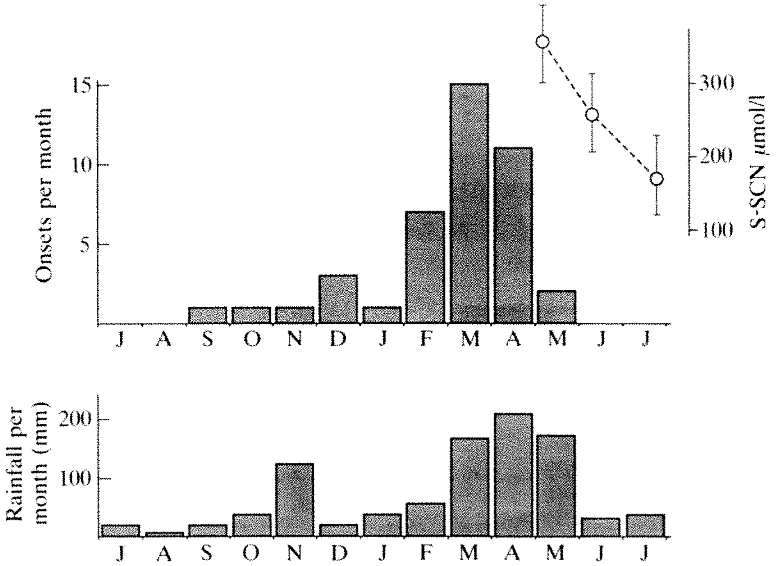

FIG. 3. The number of onsets of spastic paraparesis per month in studied villages, mean serum thiocyanate (±SEM) in μmol/l in examined cases, and rainfall at Shirati Hospital in mm per month from July 1984 to June 1985.

was positive in 8 of 18 cases tested and in 3 out of 8 family members tested. Mean total protein in serum was 67 g/l in the cases and 65 g/l in the family members, which is within the reference limits used at the Tanzanian laboratory.

DISCUSSION

The main contribution of this study is the detailed clinical investigation of cases of spastic paraparesis during the epidemic shortly after onset, with follow-up examinations 1, 10 and 36 months later. The neurological findings were uniform and were almost identical to those reported from Mozambique (Ministry of Health, 1984*a*) and Zaire (Trolli, 1938; Lucasse, 1952; Carton *et al.*, 1986). These reports can only be interpreted as describing a distinct disease entity, konzo, characterized by symmetric isolated bilateral involvement of upper motor neurons of abrupt onset. The damage is permanent but not progressive. The syndrome varies in severity but always affects upper motor neurons with longer axons to a greater extent than those with shorter axons. The disease spectrum varies from hyperreflexia in the legs to severe spastic paraparesis with associated weakness of the trunk and arms. This is sometimes accompanied by dysarthria and optic atrophy. Mild sensory symptoms at the onset seem to clear during the first month, but signs of upper motor neuron damage remain unchanged despite some functional improvement in the first few months.

There are some minor differences in the clinical findings between the studies of konzo in Mozambique, Zaire and Tanzania. The absence of difficulty in hearing in the 39

Tanzanian cases may be explained by the infrequency of this sign, only 2 of 20 Zairian cases (Carton *et al.*, 1986) and 1 out of 53 Mozambican cases (Ministry of Health, 1984*a*) had hearing impairment. Diminished visual acuity is reported in all three studies, and the difference in frequency of optic atrophy may be explained by the variation of ophthalmological signs over time found in the present study. Slight sensory symptoms were reported in a few cases with recent onset in Mozambique but were absent in the cases examined several years after onset in Zaire. This is in accordance with the findings in this study of sensory symptoms at onset which are clearing during the first month. Extensor plantar responses were not found in Mozambican cases (Ministry of Health, 1984*a*) or in the first study in Zaire (Trolli, 1938), which is in sharp contrast to later findings in Zaire (Carton *et al.*, 1986) and in the present study. Quite apart from the difficulties in eliciting the Babinski sign in heavily calloused feet, it was found difficult to elicit the sign without putting the patients into a lying position with extended legs. The marked plantar flexion and valgus deformity of the feet also contributed to the difficulties in interpretation, which may explain the differences between the studies. Apart from these minor differences, identical findings have now been reported from outbreaks of spastic paraparesis from three geographically widely separated areas of Africa. We find it reasonable and practical to use the name konzo for this disease. It is the local name used by the affected population first studied by Trolli (1938).

Although the same probable aetiological role of cassava toxicity has independently been advanced from studies in all three countries affected, the cause of konzo is still not fully defined. An infectious cause was in fact first suspected in all outbreaks studied but so far no infectious agent has been identified as a possible candidate. Clustering of cases in families was regarded as a strong indication of infectious aetiology by Carton *et al.* (1986). The same clustering in families was found in the present study but it is fully consistent with dietary aetiology although it may indicate a predisposing factor. Signs of infection such as fever, respiratory or intestinal symptoms were lacking in this study, and no laboratory support for aetiological involvement of syphilis, schistosomiasis or HTLV-I was found. The tropical spastic paraparesis associated with HTLV-I (Roman, 1987; Anonymous, 1988) differs from the disease under study in its gradual onset, progressive course and limitation to adulthood. This clinical difference in combination with the absence of HTLV-I antibodies in the konzo cases from Tanzania and Zaire (Rosling *et al.*, 1988) strongly indicates that konzo and HTLV-I-associated tropical spastic paraparesis are different disease entities. Konzo also differs clinically from other tropical myelopathy syndromes (Cruickshank, 1976) by its uniform clinical picture of abrupt onset, selective upper motor neuron damage and wide age distribution. Certain common epidemiological features of all reported outbreaks of konzo differ from those found in the other forms of tropical myelopathies. First, the disease has only been reported from cassava-eating rural populations. Secondly, the acute outbreaks of the disease coincide with periods of food shortage when the diet consists almost entirely of roots and leaves from toxic cassava varieties and when availability of supplementary food is limited.

Dietary cyanide exposure from cassava is a probable aetiological factor in konzo. Cassava roots and leaves contain cyanogenic glucosides that on hydrolysis yield cyanide, which in the human body is converted to the far less toxic substance thiocyanate (Rosling, 1986). Toxic varieties are grown as staple crops because of their higher yields, and drought increases the glucoside levels in these varieties (Ministry of Health, Mozambique, 1984*b*). Populations consuming cassava use various processing methods to remove cyanide before consumption. The special processing method used by the present affected population has to our knowledge never been studied nor described in the literature. It can be expected that it is ineffective in removing cyanide since the disintegration of root tissue is incomplete (Lancaster *et al.*, 1982). At the time of the outbreak the removal of cyanide was still more ineffective since the processing was shortened due to lack of food.

A high dietary cyanide exposure in the cases at the onset is supported by the serum thiocyanate level, 368 μmol/l found in the cases examined in May 1985. This is eight times the mean level in a reference population (Lundquist *et al.*, 1979) but corresponds to the level reported in konzo cases in Mozambique, 329 μmol/l (Ministry of Health, 1984*a*). These levels are in fact higher than any previously reported from populations exposed to cyanide from inadequately processed toxic cassava, including the thiocyanate levels reported to aggravate goitre in cassava eating populations by interfering with the iodine absorption in the thyroid gland (Delange *et al.*, 1982). The absence of goitre in the presently studied population may be explained by an adequate iodine intake which has been shown to quench the goitrogenic effect of even high thiocyanate loads (Cliff *et al.*, 1986).

A pronounced seasonal variation of cyanide exposure, measured as thiocyanate levels, with peaking during the period of the epidemic was found in Mozambique (Casadei *et al.*, 1986). The same pattern was found in this study, with the highest values in cases studied in May and falling levels in June and July 1985 (fig. 3). Cyanide exposure may only be indirectly involved in the damage to motor neurons in konzo. A diet exclusively of cassava, which is associated with the outbreaks of konzo, is very low in protein, and thus in sulphur amino acids (Lancaster *et al.*, 1982) which provide the sulphur substrate for conversion of cyanide to thiocyanate. The combination of high cyanide and low sulphur intake may result in deficient formation of sulphur compounds essential for the function of motor neurons, secondary to preferential use of sulphur for cyanide detoxication (Cliff *et al.*, 1985).

Another tropical myelopathy associated with dietary cyanide exposure from cassava is tropical ataxic neuropathy (TAN). It is a disorder described from Nigeria (Osuntokun, 1968) and Tanzania (Makene and Wilson, 1972) and is characterized by gradual onset of posterior column symptoms in older adults, often in combination with peripheral neuropathy, optic atrophy, nerve deafness and sometimes spastic paraparesis. TAN thus differs both clinically and epidemiologically from konzo and from tropical spastic paraparesis. In spite of the differences between these three entities the epidemic of konzo in Mozambique was classified as a form of TAN, and konzo in Zaire as tropical spastic paraparesis in a recent review (Román, 1987). The cyanide exposure in TAN cases, measured as serum thiocyanate, was considerably lower than that found in konzo cases in Mozambique and Tanzania. The apparent contradiction between two different clinical forms of myelopathy being attributed to dietary cyanide exposure from cassava may be explained by a different rate of exposure to the toxin, high levels during a short period resulting in acute upper motor neuron damage and lower levels over a longer period resulting in a more complex myelopathy. A similar mechanism has in fact been suggested to explain the two different conditions, early onset amyotrophic lateral sclerosis and late onset parkinsonism dementia associated with neurotoxic effects of the amino acid beta-N-methylamino-L-alanine (L-BMAA) in the plant *Cycas circinalis* consumed in Western Pacific Islands (Spencer *et al.*, 1987). The cases of konzo in this study that were followed for 3 yrs did not develop optic atrophy or other symptoms of TAN. Further follow-up studies will reveal if TAN cases will appear in this or other populations affected by konzo.

Lathyrism is the tropical myelopathy most similar to konzo, except for the absence of visual disturbances. It is characterized by the same acute onset of permanent selective damage to the upper motor neurons affecting the same age group in epidemics during food shortage periods. Lathyrism is caused by high consumption of the drought-resistant chickling pea, *Lathyrus sativus*, a crop which does not exist in any of the areas affected by konzo. The overall similarity between lathyrism and konzo suggests a similar or common final pathogenic mechanism. Recent experimental work has shown that the excitatory amino acid beta-N-oxalylamino-L-alanine (BOAA) found in the chickling pea and having chemical relationship to L-BMAA is likely to be causally associated with lathyrism (Spencer *et al.*, 1986). It should be noted in this context that longstanding high cyanide levels result in reactions between cyanide and cysteine residues in albumin, and probably also in other body proteins, yielding aminothiazolidine carboxylic acid which has structural similarities with the toxic amino acid associated with lathyrism (Lundqvist *et al.*, 1985; Rosling, 1986). It could thus be hypothesized that this substance causes damage to motor neurons in a similar way as proposed in lathyrism and the motor neuron disease described from the Western Pacific.

The aetiological hypothesis for konzo needs to be confirmed by a dietary intervention study in some of the affected areas and in an animal model. Meanwhile the present evidences are strong enough to try to prevent konzo by promoting regular use of effective processing methods for cassava and securing at least minimal availability of supplementary foods in populations at risk. There are many public health parallels between konzo and beri-beri as well as pellagra, diseases that were not controlled by abolishing or even decreasing rice and maize cultivation, respectively. Promotion of cassava cultivation with improved varieties and with cultivation methods that restore soil fertility may in fact be the most appropriate first step to improve socioeconomic and dietary conditions and thereby prevent konzo in the famine-threatened African populations at risk. Quite apart from these important public health aspects, a further elucidation of this motor neuron disease may provide new input to neuroscience.

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CEREBRAL CONTROL OF DIRECTED VISUAL ATTENTION AND ORIENTING SACCADES

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SUMMARY

The object of this experiment was to identify the contribution of the frontal and parietal lobes to the control of visual attention and voluntary saccades. A symbolic spatial cue (arrow) was used to indicate validly or invalidly the location of a visual target located to the left or right of the cue. Manual reaction time and reaction time to initiate a saccade to the target were measured. Patients with damage to the left frontal lobe ($n = 6$), right frontal lobe ($n = 7$) and right parietal lobe ($n = 7$) were compared with normal control subjects ($n = 20$). A sex difference was found for the right cerebral hemisphere patients in the manual reaction time data. Right parietal males and right frontal females showed an overall elevation in manual reaction time, reflecting an inability to maintain a normal level of visual arousal and/or motor activation. Conversely, right frontal males and right parietal females were not influenced significantly by cue validity, suggesting that they were unable to direct visual attention in a covert manner. All subjects showed a normal effect of cue validity on saccade reaction time. Thus the cortical areas studied do not appear to be necessary for directing visual attention with a saccade. Cue validity, however, affected saccade amplitude, especially in the left visual field of patients with right hemisphere damage. The cue validity effect depended both on the sex of the subject and the anterior/posterior location of damage in the right hemisphere. Damage to the right frontal lobe resulted in an 'under' reaction to the spatial cues, especially in the male patients. Saccades were smaller than normal following the valid cues, but larger than normal following the invalid cues. The effect was opposite following damage to the right parietal lobe. In this case, saccade amplitude reflected an 'over' reaction to the spatial cues, especially in the female patients. Saccades were larger than normal following valid cues and smaller than normal following invalid cues.

INTRODUCTION

Unilateral neglect is caused by damage to certain regions of the central nervous system. Riddoch (1935) and Brain (1941) described patients who, despite normal visual acuity, displayed symptoms of visual disorientation (e.g., defective localization of objects in space, visual-object agnosia, loss of topographical memory) limited to homonymous hemifields. Brain suggested that these symptoms were due to inattention to external space contralateral to the cerebral damage. In severe cases these patients behave as though the half of space opposite to the side of their cerebral damage does not exist. A patient may groom and dress one side of his body only or may fail to eat the food located on

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the neglected side of his plate (Patterson and Zangwill, 1944; McFie *et al.*, 1950). Most patients with neglect due to a stable lesion improve with time. Associated with this improvement is the less severe symptom of sensory extinction. In the case of neglect, contralateral stimuli are ignored under most conditions; in sensory extinction, contralateral stimuli are ignored only with simultaneous bilateral stimulation. Unilateral neglect and/or sensory extinction have been reported in monkeys and humans following damage to the frontal lobe (Kennard, 1939; Welch and Stuteville, 1958; Heilman and Valenstein, 1972; Watson *et al.*, 1978; Damasio *et al.*, 1980) and the parietal lobe (Brain, 1941; Costa *et al.*, 1969; Heilman *et al.*, 1970; Chédru *et al.*, 1973; Hausser *et al.*, 1980; Posner *et al.*, 1984). Considerable evidence in the monkey literature suggests that these cortical regions work together to control different aspects of directed attention to extrapersonal space.

Several models of visual attention and orientation have recently appeared in the literature (Heilman and Watson, 1977; Mesulam, 1981; Butter, 1987). The model of Heilman and Watson postulates that visual attention and orientation are mediated by a single but complex circuit. They propose that unilateral neglect is primarily the result of reduced arousal leading to an inability to prepare for action (hypokinesia). These conditions are due to a defect in a corticolimbic reticular loop. The cortex stimulates the mesencephalic reticular formation when a stimulus is relevant (i.e., novel or biologically significant). In turn, the reticular formation increases sensory arousal via ascending cortical connections or by inhibiting the thalamic reticular nuclei (Watson *et al.*, 1981). Watson *et al.* suggested that the posterior parietal cortex, via its connection with posterior cingulate cortex, determines the significance of a stimulus. Prefrontal cortex, via its connection with anterior cingulate cortex, prepares voluntary responses. In a model that is similar to that of Watson *et al.*, Mesulam (1981) suggested that posterior parietal cortex, via its relationship with cingulate cortex, is involved in determining the personal relevance of a stimulus. In addition, he proposed that posterior parietal cortex provides a sensory representation of extrapersonal space. This internal representation, along with information regarding stimulus relevance, is used to control spatial shifts of attention. Butter (1987) proposed that visual attention and orientation are mediated by a single, polysensory system of anatomically-connected structures and that each of these structures (including frontal and parietal cortex) contributes in some way to the control of both shifts of attention and overt (observable) orienting movements. Butter's model postulates that the role of frontal cortex (specifically, frontal eye fields) is to suppress orienting eye movements to salient but irrelevant stimuli. A recent case study supports this hypothesis (Butter *et al.*, 1988).

A primary distinction between the above models is the role hypothesized for posterior parietal cortex. Butter suggested that posterior parietal cortex controls some aspect of observable orienting movements, while Heilman and Watson and Mesulam suggested that the control exerted by this region is independent of observable movement.

The models proposed by Watson *et al.* (1981) and Mesulam (1981) are supported by studies of the neuronal characteristics of dorsolateral frontal and posterior parietal cortex in behaving monkeys (*see* Wurtz *et al.*, 1980). Neurons were identified in each area which yield enhanced responses (i.e., increased discharge or prolonged response) to visual stimuli of relevance to the monkey. The enhancement effect seen in frontal cortex was response dependent, occurring only when an orienting saccade was made to a stimulus. Neurons in parietal cortex showed enhancement to motivationally-significant stimuli (i.e., stimuli associated with reward) even when these stimuli were not fixated. In terms of behavioural relevance, Wurtz *et al.* speculated that the posterior parietal cortex contributes to the process of selective visual attention by facilitating motivationally-significant afferent signals independent of movement while the frontal cortex may play a role in directed attention related specifically to eye movements. In contrast, Mountcastle *et al.* (1975) have argued that the neuronal characteristics of posterior parietal cortex indicate that this region plays a role in commanding eye movements to stimuli in space. This review supports the model proposed by Butter (1987).

The role of dorsolateral frontal cortex in the control of saccadic eye movements, fixation stability and visual search has been investigated with different methods in both monkeys (Bizzi and Schiller, 1970; Latto and Cowey, 1971; Latto, 1978; Marrocco, 1978; Schiller *et al.*, 1979, 1980) and man (Rasmussen and Penfield, 1948; Karpov *et al.*, 1968; Melamed and Larsen, 1979; Guitton *et al.*, 1985). Acute unilateral lesions in the frontal lobe are associated with ipsilateral deviation of the head and eyes and an inability to direct gaze contralaterally on command (Holmes, 1918; Chédru *et al.*, 1973). Chronic unilateral lesions of the frontal lobe may hinder a patient's ability to find a visual target appearing in the contralateral visual field (Teuber, 1964) and this increase in visual search time may be due to the disorganization of active search patterns (Karpov *et al.*, 1968; Daroff and Hoyt, 1971) or to an inability to suppress inappropriate reflex-like saccades (Guitton *et al.*, 1985; Butter *et al.*, 1988). However, the role of dorsolateral frontal cortex in the control of saccades remains unclear. Also, the functional relationship between the mechanisms controlling saccadic eye movement and directed visual attention needs clarification (e.g., Klein, 1980).

Little is understood about the disrupted mechanisms underlying hemispatial neglect caused by posterior parietal damage. Some data point to a disruption of saccadic eye movement control following parietal damage (Chédru *et al.*, 1973; Baloh *et al.*, 1980; Johnston, 1983). Studies of patients with homonymous hemianopia (Gassel and Williams, 1963; Cohn, 1972; Messert and Barron, 1973; Meienberg *et al.*, 1981) indicated that the saccade system works to compensate for a visual field defect by adjusting the direction of gaze so that a target appears in a functional region of the visual field. Studies that have focused on the relationships between saccadic eye movement control, severity of hemispatial neglect and visual field defects (Chédru *et al.*, 1973; Johnston, 1983) have indicated that disruption of saccadic behaviour (e.g., increased visual search times and saccade dysmetria) may be more closely related to the presence of a visual field defect than to the severity of hemispatial neglect. However, data from one of these studies (Johnston, 1983) suggest that a complex relationship exists between the mechanisms that control saccades and those underlying hemispatial neglect. The nature of this relationship needs clarification.

Other data suggest that parietal visual neglect is caused by visual spatial disorientation (Karpov *et al.*, 1968; Rosenberger, 1974; Girotti *et al.*, 1983), by a disruption of the internal representation of external space or its access (Butters and Barton, 1970; Bisiach and Luzzatti, 1978; Bisiach *et al.*, 1979, 1981), by a postperceptual, preverbal loss of awareness of visual field stimuli (Volpe *et al.*, 1979) and/or by a disruption in the ability to disengage from visual field stimuli (Posner *et al.*, 1984).

Previous studies of directed visual attention and orientation following cerebral damage in patients have looked for relationships between homonymous hemianopia, sensory extinction or hemispatial neglect and some of the symptoms mentioned in the previous paragraphs. Possible differences between frontal and parietal lobe mechanisms were not considered in these studies. In most cases the lesions were large and included both regions.

The present study has attempted to clarify the contribution of anterior and posterior cortical systems to mechanisms of visual attention and orientation. Two tasks were used to measure the ability to shift attention with or without orienting saccades (Posner, 1980; Posner and Cohen, 1980). This was achieved by manipulating the validity of a symbolic spatial cue (an arrow) that pointed either towards the visual field where a target light appeared or to the opposite visual field. In previous studies (e.g., Posner, 1980) it was demonstrated that normal subjects respond faster to a target light when a cue preceding the target points to the side where it will appear (valid cue condition). When the cue points to the opposite side (invalid cue condition), normal subjects respond more slowly. Therefore the validity of a spatial cue affects how quickly a subject will detect and respond to the target. A significant difference in reaction times between valid and invalid cue conditions is used to define attention operationally, directed selectively to one visual field. The absence of an effect of cue validity on reaction time was assumed to indicate a disruption of this attentional process.

In a recent study, Posner *et al.* (1984) used a similar paradigm to test patients with cerebral damage. Several differences in methodology exist between Posner's study and the present study. Only 3 of the 13 patients with parietal lesions in the Posner study were tested with a central (as opposed to peripheral) cue. The present experiment used a central symbolic cue exclusively. Since eye movements were not monitored in the Posner study, there was no way of ensuring that central fixation was maintained. The present study was designed to compare directly the effects of selective unilateral damage to the frontal lobe or parietal lobe, whereas the Posner study combined patients with frontal and temporal lobe damage into one group. In the present study, the control group consisted of normal subjects.

Sex differences in behavioural and morphological cerebral asymmetries have received much attention in recent years (*see* Robinson *et al.*, 1983). There is also evidence to suggest that the organization of the left hemisphere differs between sexes (Kimura, 1983; Ojemann, 1983). Therefore sex has been included as a factor in the present investigation in order to assess its effect on mechanisms of visual attention and orientation following cerebral damage.

METHODS AND SUBJECTS

General design

Experiment 1 of this study used a task designed to measure a subject's ability to direct attention to a particular region of space, even in the absence of physical orientation (i.e., making a head or eye movement) to that region. The subjects were required to close a microswitch held in the hand as quickly as possible in response to the illumination of a light-emitting diode (LED) presented to the left or right of fixation. Normal subjects used their dominant right hand, while the neurological subjects used the hand ipsilateral to the side of their cerebral damage.

Experiment 2 measured the allocation of overt visual attention (i.e., resulting in an orienting saccade) to a particular region of space and the control of an orienting saccade to an attended versus unattended region of space. The subjects were required to look directly at the LED target as quickly as possible in response to its illumination.

For each experiment an arrow cue indicating the probable location of the target light appeared at the fixation site shortly after the onset of each trial. There were four trial types, referred to as 'valid', 'neutral', 'invalid' and 'catch' trials. In the valid trial condition the arrow cue pointed accurately to the side where the target light appeared. In the neutral trial condition the target light was preceded by a double arrow pointing in both directions. The arrow cue pointed to the side opposite to the target light in the invalid trial condition. On catch trials, the cue was not followed by a target light. The catch trials were included to ensure that the subjects responded to the illumination of the target light and not to a temporal interval after presentation of the arrow cue.

It has been demonstrated (e.g., Posner, 1978, 1980; Posner and Cohen, 1980) that normal subjects detect and respond faster to a visual target that appears in the visual field where it is expected than to a visual target that appears in the opposite visual field. A significant difference in the reaction times for an expected target and an unexpected target provides an operational measure of directed visual attention. Although it is operationally difficult to create a truly neutral condition (Jonides and Mack, 1984), one was included in the hope of measuring both the cue benefit (reaction time for neutral condition minus reaction time for valid cue condition) and cue cost (reaction time for invalid condition minus reaction time for neutral condition). It was predicted that if a cerebral region was critical to the process of directing visual attention and gaze, damage to this region would result in effects of cue validity that differed significantly from its effects on the performance of normal subjects. If the normal subject data indicated significant effects of both cue benefit (reaction time for neutral condition minus reaction time for valid cue condition) and cue cost (reaction time for invalid cue condition minus reaction time for neutral cue condition), then the effects of cerebral lesions on both the engagement and disengagement of attention could be assessed directly. However, this was not the case. Analysis of cue validity effects therefore focused on the valid and invalid cue conditions. In this case, the lack of a significant effect of cue validity (invalid condition minus valid condition) for a particular group suggested that the damaged region is critical for maintaining directed attention and/or gaze. The visual field in which the target was presented was included as an experimental factor to assess whether any behavioural changes were selective to one visual field.

The subjects attended two sessions which occurred approximately 2 wks apart. At each session 22 practice trials and 120 experimental trials were collected for each experimental task (manual reaction time with central fixation for Experiment 1, followed by the saccade reaction time for Experiment 2). Of the experimental trials, 128 (64%) used valid cues, 40 (20%) neutral cues and 32 (16%) invalid cues. There was a total of 40 catch trials. For each of the cue conditions, the stimulus location was equally and randomly divided between the left and right visual fields. The occurrence of each of the trial types was randomized with the restriction that no trial type occurred more than twice in succession. Eye movements were measured by an electro-oculographic (EOG) method and the EOG signal was analysed on-line by a computer. Each subject's manual or saccade reaction time (time between the onset of the target light and the response) was measured and recorded. For Experiment 2 each saccade was also characterized by its amplitude, duration and peak velocity. Attempts were made to match subjects for age, education, and socioeconomic level. Neurological and neuropsychological assessments were performed to allow evaluation of factors which, in addition to site of cerebral damage, could influence a neurological subject's performance (e.g., amount of cerebral damage, age of lesions, aetiology of cerebral damage, language deficit, visual-field defect).

Subjects

All subjects in this study participated on a voluntary basis. Normal subjects (10 female, 10 male) were recruited from hospital personnel. Each met the following criteria: vision of normal acuity (20/40) with or without corrective lenses, no history of neurological dysfunction (e.g., loss of consciousness, seizures, sensory/motor changes, head trauma, memory or learning problems), no history of drug abuse or psychiatric hospitalization, free of medication or drugs known to affect the oculomotor system (Leigh and Zee, 1983, p. 44), an IQ of at least 90 (average) as estimated by the Peabody Picture Vocabulary Test (Dunn, 1959), and normal performance on the Purdue Pegboard Test (Rapin *et al.*, 1966) and Symbol-Digit Modalities Test (Smith, 1968), two sensitive measures of cerebral dysfunction. Patients were selected from lists, covering a 2 yr period, reviewed in the Neurology and Neurosurgery departments of Henry Ford Hospital in Detroit. The combined daily census of inpatients over this period averaged approximately 75. The medical record of a patient was reviewed if the discharge diagnosis suggested that he or she met the study objective. A patient was approached by letter if he or she had sustained focal damage to one of the critical cerebral regions, had no history of psychiatric hospitalization or drug abuse and was free of symptoms suggesting vestibular, cerebellar, cranial nerve III, IV or VI dysfunction or medial longitudinal fasciculus syndrome. Informed consent was obtained from each subject. Nineteen patients who agreed to participate in the study did not complete the experimental testing. None of the subjects exhibited symptoms of hemispatial neglect at the time of testing, although some had exhibited it to varying degrees during the acute stage of their illness. Each patient was assigned to one of three groups based on the site of their cerebral damage assessed by CT: unilateral left frontal lobe, right frontal lobe or right parietal lobe. The underlying aetiologies included encephalomalacias secondary to vascular disease, primary neoplasm (astrocytoma) with subsequent surgical removal, focal cerebritis with subsequent abscess removal, and depressed skull fracture with focal cortical damage. All lesions were of long-standing (greater than 4 mos). The neuropsychological status of each patient was assessed by the following tests: Symbol-Digit Modalities Test (Smith, 1968), Trail Making Tests (Armitage, 1946; Reitan and Tarshes, 1959), Purdue Pegboard (Rapin *et al.*, 1966), Peabody Picture Vocabulary Test (Dunn, 1959), Token Test (De Renzi and Vignolo, 1962), Wingfield Object Naming (Oldfield and Wingfield, 1965), Wechsler Adult Intelligence Scale Revised; Information, Comprehension and Object Assembly subtests (Wechsler, 1981) and the Wechsler Memory Scale-Form 1 (Wechsler, 1945). Neglect was assessed by measures of visual scanning, double simultaneous tactile stimulation and line bisection. Stereognosis and right/left identification (Frederiks, 1969*a*, *b*) were also evaluated. A questionnaire was used to evaluate the hand preference of each subject (Annett, 1970).

Apparatus and stimulus conditions

Subjects were seated in a dimly illuminated room at a distance of 57 cm from a panel (60 cm × 76 cm) on which the red fixation light, arrow cues and target lights appeared along a horizontal line at eye level. A 5 × 7 dot matrix light (subtending 2° of visual angle) was programmed to create a left arrow, right arrow or double arrow (*see* fig. 1). The target lights (subtending 0.5° of visual angle) were located 10° left and right of fixation and they were of equal luminance. White noise (70 dB) was used to mask extraneous sounds.

A microcomputer (AIM-65) was used to control stimulus events (*see* fig. 1) and monitor subject responses. A warning tone of 0.5 s preceded the cue presentation by a random variable interval of 0.5–3 s. The duration of the arrow cue was 50 ms. It was followed 150 ms later by the target light, creating a stimulus onset asynchrony of 200 ms. The target light remained on until either a manual response (Experiment 1) or a saccade (Experiment 2) occurred or until the maximum allowed response time (2 s) elapsed. The trial sequence was initiated by the experimenter when central fixation was stable.

Based on early pilot data collected from young normal subjects (mean age 18 yrs) for Experiment 1, a manual reaction time of less than 200 ms was considered anticipatory and the trial was repeated later

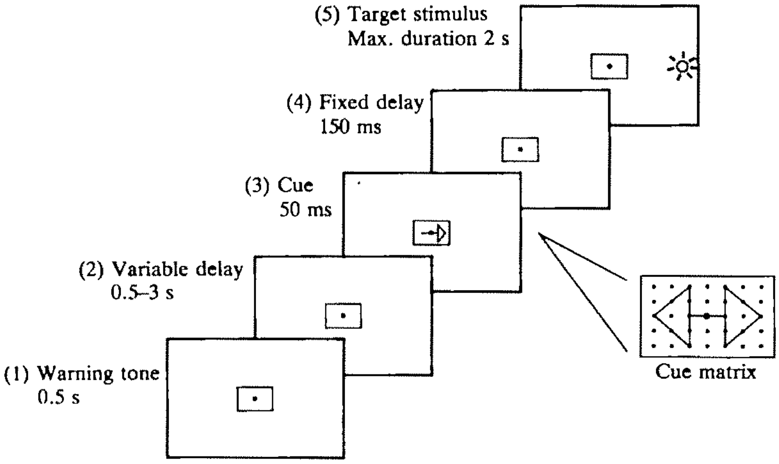


FIG. 1. Diagrammatic representation of trial sequence.

in the session (reaction times of approximately 200 ms represented the 25th percentile for the valid cue condition in these data). Using the same criterion, 120 ms was used as the lower limit for saccade reaction times in Experiment 2. These limits may have been too low for the slower responding older subjects in this study. However, the catch trial data indicated that this condition was effective in establishing the psychological set to wait for target onset before orienting to the target. For Experiment 1 less than 20% of catch trials resulted in a manual response. For Experiment 2 the saccade reaction times of false positive errors were very long, and most likely represent moments when maintenance of fixation became difficult (normal female, $\bar{X}$ = 847 ms, SEM = 88, range 161–1,589; normal male, $\bar{X}$ = 909 ms, SEM = 92, range 286–1,674). A total of 23/177 (13%) false positive errors were characterized by reaction times short enough to represent anticipatory responses. Therefore only 0.02% of all catch trials resulted in saccades that might be considered anticipatory. The overall mean of these trials was 224 ms (normal female, $\bar{X}$ = 161 ms; normal male, $\bar{X}$ = 286 ms). Since it appears that anticipatory responses occurred at a level far below chance, the possible inclusion of some of these trials would have had no significant and systematic effect on the results. In addition, a trial was repeated if no response occurred within 2 s, an eye blink occurred, or if a saccade was made away from central fixation before the manual response. A trial was repeated in Experiment 2 if an eye blink occurred, eye movement was made away from central fixation during a catch trial or if a saccade was made away from the side of stimulus presentation.

Procedure

Each session began with approximately 2 h of clinical neuropsychological testing. Before the experimental testing the subjects were given detailed instructions regarding the trial sequence, the meaning of the arrow cues and the probability that they would be accurate, and the required response. They were told to respond as quickly as possible after the appearance of the target light, but cautioned against responding to an event preceding that target. The subjects were shown each cue type and then were asked to identify them when presented randomly. The subjects were given 1 to 3 blocks of 9 trials each to correctly identify each of the cues 3 times within each block. Each type of trial, including both the cue and target light, was then presented. Eye movements were calibrated by having the subjects alternate their point of fixation between the fixation light and the left and right target lights. Subjects received 22 practice trials and then 2 blocks of 60 trials each. A 5 min rest period occurred between blocks. If necessary, recalibration of the EOG was performed between the blocks.

Eye movement measurement

Horizontal eye movements were measured by the EOG technique (*see* Shackel, 1967; Oster and Stern, 1980). Miniature silver-silver chloride electrodes were placed at the outer canthus of each eye with a reference electrode at the centre of the forehead. Vertical eye movements were not monitored. Subjects were asked to refrain from blinking after they had heard the tone indicating the onset of a trial. When eye blinks did occur, they were typically characterized by a large peak velocity (>1000 deg/s) and short duration (2 – 10 ms). Subjects were seated with their heads stabilized with chin, forehead and temple supports. The EOG signal was fed into a differential d.c. preamplifier, the output of which was monitored on an oscilloscope and also directed to the AIM-65 computer where the signal was filtered with a low-pass analogue filter (roll-off: 12 dB/octave). The Nyquist frequency cut-off for this filter was set at 120 Hz which meant that there was no signal attenuation from 0 to 40 Hz. The filtered analogue signal was digitized and fed to the computer for on-line analysis. Eye position was sampled at 1 ms intervals with a resolution of approximately 10 min of arc (6.4 A/D counts = 1° of visual angle).

As each new 1 ms sample was taken, the 30 most recent sample values were averaged in successive groups of 5 ms, and the successive differences between the 6 averaged A/D count values were computed. Each difference value was then checked to determine whether it exceeded a 'noise level' difference of ±2 A/D counts or a 'criterion level' difference of ±4 A/D counts.

The start of an eye movement was defined as the start of a 30 ms sample series in which (1) at least 3 averaged difference values exceeded criterion level and had the same sign, and (2) no more than 1 of the remaining two difference values exceeded the noise level with the opposite sign. The end of an eye movement was defined as the start of a 30 ms sample series in which (1) 2 or more difference values exceeded criterion level and were opposite in sign to the direction at the start of the eye movement or (2) fewer than 3 difference values exceeded the noise level in the same direction as the eye movement. During the eye movement, difference values were calculated in successive 1 ms samples and the largest value and its temporal value were recorded for later analysis along with the trial type, trial outcome, peak velocity value and time and the time and position at the beginning and end of any eye movement. These summary data and all of the averaged 5 ms A/D samples collected for each eye movement were stored on disc for later analysis.

RESULTS

The primary method of data analysis used was a 4-way repeated measures ANOVA (Winer, 1971). Grouping factors were subject group and sex. Within-subject factors were visual field of target presentation and cue validity. The 5 dependent variables were median manual reaction time for Experiment 1 and median saccade reaction time, mean saccade amplitude, mean saccade duration and mean saccade peak velocity for Experiment 2. Since the neutral cue did not provide a measure of both cue benefits and costs, the cue validity factor was assessed using the valid and invalid trials. The Scheffé procedure (Winer, 1971, p. 196) was used to calculate 95% confidence intervals for post hoc pairwise and multiple, complex contrasts between group means. Trials resulting in a response error were infrequent, and few systematic differences as a function of the experimental conditions were found for these trials.

Experiment 1

When the data of normal subjects (Table 1) were analysed alone, significant effect were found for sex and cue validity. Females (n = 10) in this study were significantly slower than males (n = 10) (560 ms vs 493 ms; F(1/18) = 4.25, P = 0.05). The overall

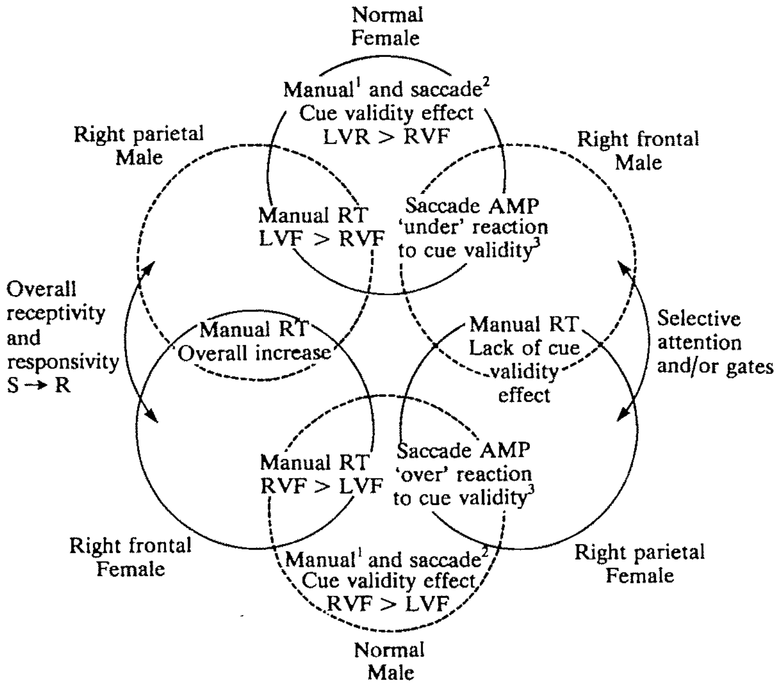
TABLE 1. MEDIAN MANUAL REACTION TIMES (ms) FOR VALID, NEUTRAL AND INVALID CUE TRIALS: NORMAL SUBJECTS

	Left visual field			*Right visual field*		
	Valid	*Neutral*	*Invalid*	*Valid*	*Neutral*	*Invalid*
Female						
NF1	501	591	545	504	553	490
NF2	663	662	675	674	683	674
NF3	465	495	493	459	483	498
NF4	590	601	623	576	610	582
NF5	538	550	567	528	559	570
NF6	488	509	496	474	494	518
NF7	448	500	546	447	469	501
NF8	589	622	614	571	626	624
NF9	627	646	620	642	614	639
NF10	540	566	579	516	547	549
Mean	*545*	*574*	*576*	*539*	*564*	*565*
SD	*71*	*60*	*58*	*76*	*70*	*65*
Male						
NM1	456	508	494	437	481	474
NM2	503	551	472	505	536	552
NM3	422	456	426	410	414	456
NM4	406	399	395	400	418	427
NM5	517	605	595	543	565	577
NM6	562	615	639	558	600	615
NM7	429	478	471	455	497	530
NM8	383	441	432	364	425	395
NM9	602	614	623	593	608	691
NM10	402	412	406	413	420	480
Mean	*468*	*508*	*495*	*468*	*496*	*520*
SD	*74*	*84*	*91*	*77*	*77*	*91*
Overall						
Mean	*507*	*541*	*536*	*503*	*530*	*542*
SD	*81*	*79*	*85*	*83*	*79*	*80*

effect of cue validity was significant (F(2/36) = 29.59, $P < 0.01$). This cue validity effect was due to a significant overall effect of cue benefit (30.8 ms), but not cue cost (−2.5 ms). However, analysis of the valid and invalid trials indicated a significant effect of cue validity (F(1/18) = 49.05, $P < 0.01$) and established these conditions as reliable operational measures of directed attention.

When data from the neutral cue condition were dropped from the analysis of normal subjects, the Sex × Visual Field × Cue Validity interaction approached significance (F(1/18) = 3.29, $P = 0.09$). The normal males tended to show a greater effect of cue validity to stimuli appearing in their right than in their left visual field, while the opposite pattern was found for the normal females. A significant Sex × Visual Field interaction also emerged (F(1/18) = 4.38, $P = 0.05$). As shown in fig. 6, females responded more slowly to stimuli in the left than in the right visual field, while males showed the opposite pattern (*see* fig. 2, top and bottom).

Analysis of normal (Table 1) and neurological subjects (Table 2) indicated a significant effect of Lesion (F(3/32) = 3.67, $P < 0.03$), Sex (F(1/32) = 5.12, $P < 0.04$) and Cue Validity (F(2/64) = 33.85, $P < 0.01$). Overall, the right frontal (n = 7) and right


Normal Female
Manual[1] and saccade[2] Cue validity effect LVR > RVF
Right parietal Male
Right frontal Male
Manual RT LVF > RVF
Saccade AMP 'under' reaction to cue validity[3]
Overall receptivity and responsivity S → R
Manual RT Overall increase
Manual RT Lack of cue validity effect
Selective attention and/or gates
Manual RT RVF > LVF
Saccade AMP 'over' reaction to cue validity[3]
Right frontal Female
Manual[1] and saccade[2] Cue validity effect RVF > LVF
Right parietal Female
Normal Male

[1] Marginal significance (P=0.086).[2] Sex difference includes all subjects.
[3] Normal subject trend (P=0.10). RT=reaction time. LVF=left visual field.
RVF =right visual field. S→R =stimulus to response

FIG. 2. Venn diagram of sex-dependent behavioural results found in Experiments 1 and 2.

parietal patients (n = 7) responded more slowly than left frontal patients (n = 6) and normal subjects. The average of all reaction times for the right frontal and right parietal groups (601 ms) was significantly slower than the average of all reaction times for the left frontal and normal groups (529 ms) (critical difference = 68; actual difference = 72). As was the case for the normal subject analysis, the females were significantly slower than the males. The critical difference for the contrast comparing female (604 ms) and male (544 ms) overall reaction times was 46 (actual difference = 60 ms). A significant Lesion × Visual Field interaction (F(3/32) = 3.53, $P < 0.05$) resulted from the finding that the normal and right frontal groups showed no visual field difference in overall reaction time, whereas the left frontal and right parietal groups showed a significant increase in overall reaction time to stimuli appearing in the visual field contralateral to their lesion (fig. 3). Data are represented by visual field difference scores (reaction time for left visual field averaged across cue validity minus reaction time for right visual field averaged across cue validity). Positive scores reflect slower reaction times to targets in the left visual field, whereas negative scores reflect slower reaction times to targets in the right visual field. The left frontal visual field difference score (−28 ms) was

TABLE 2. MEDIAN MANUAL REACTION TIMES (ms) FOR VALID, NEUTRAL AND INVALID CUE TRIALS: NEUROLOGICAL SUBJECTS

	Left visual field			*Right visual field*		
	Valid	*Neutral*	*Invalid*	*Valid*	*Neutral*	*Invalid*
Female: left frontal						
LF1	639	691	730	670	717	745
LF2	478	505	463	493	528	536
Mean	*559*	*598*	*597*	*582*	*623*	*641*
SD	*114*	*132*	*189*	*125*	*134*	*148*
Male: left frontal						
LF3	511	519	557	560	612	640
LF4	416	427	441	410	472	456
LF5	485	556	536	515	538	565
LF6	448	472	439	456	473	432
Mean	*465*	*494*	*493*	*485*	*524*	*523*
SD	*42*	*56*	*62*	*66*	*66*	*97*
Overall Mean	*496*	*528*	*528*	*517*	*557*	*562*
Overall SD	*77*	*91*	*111*	*91*	*94*	*117*
Female: right frontal						
RF1	621	657	639	616	614	653
RF2	718	773	778	720	754	802
RF3	674	687	689	691	718	736
Mean	*671*	*706*	*702*	*676*	*695*	*730*
SD	*49*	*60*	*70*	*54*	*73*	*75*
Male: right frontal						
RF4	556	556	563	575	555	598
RF5	447	445	473	455	459	482
RF6	506	478	453	469	470	469
RF7	624	678	678	636	633	611
Mean	*533*	*539*	*542*	*534*	*529*	*540*
SD	*75*	*104*	*103*	*87*	*81*	*75*
Overall Mean	*592*	*611*	*610*	*595*	*600*	*622*
Overall SD	*95*	*120*	*119*	*102*	*114*	*123*
Female: right parietal						
RP1	551	606	579	533	531	589
RP2	510	539	523	528	543	533
RP3	629	676	683	610	624	591
RP4	511	484	471	499	510	537
Mean	*550*	*576*	*564*	*543*	*552*	*563*
SD	*56*	*83*	*91*	*47*	*50*	*32*
Male: right parietal						
RP5	663	662	677	594	613	655
RP6	655	682	698	670	702	670
RP7	617	578	685	606	649	614
Mean	*645*	*641*	*687*	*623*	*655*	*646*
SD	*25*	*55*	*11*	*41*	*45*	*29*
Mean Overall	*591*	*604*	*617*	*577*	*596*	*598*
Overall SD	*66*	*75*	*92*	*60*	*70*	*53*

contrasted with the averaged difference scores found for the remaining groups (15 ms). The critical difference for this contrast was 14 (actual difference = 43 ms). The contrast between the right parietal difference score (13 ms) and the average of the difference scores for the remaining groups (−9 ms) resulted in a critical difference of 17 (actual difference = 22 ms).

A significant Lesion×Sex interaction (F(3/32) = 3.75, $P < 0.05$) indicated that the

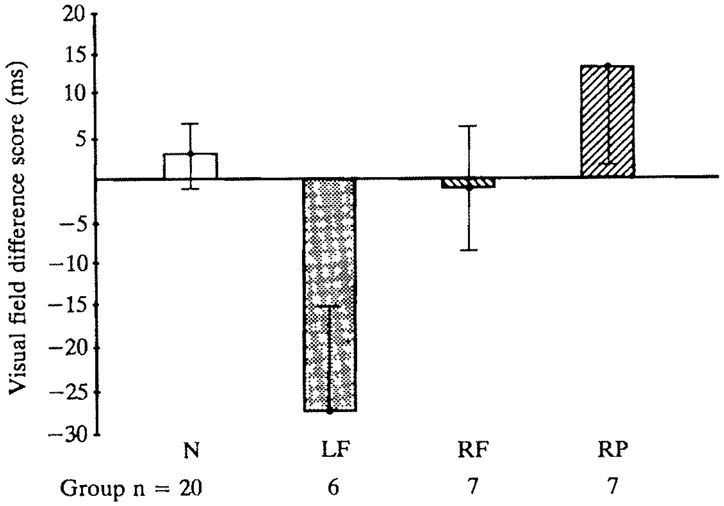


FIG. 3. Overall effect of visual field on manual reaction time: Lesion×Visual Field. Visual field effects are represented by manual reaction times to left visual field target averaged across cue validity minus reaction times to right visual field target averaged across cue validity. Positive scores represent slower reaction times to right visual field targets. Open bar = normal subjects (N); light shade = left frontal subjects (LF); downward diagonal = right frontal subjects (RF); upward diagonal = right parietal subjects (RP). SEMs are indicated by vertical bars.

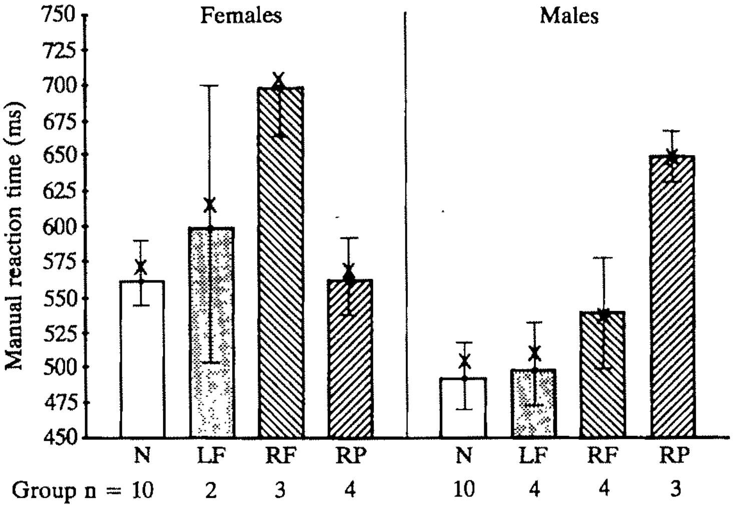


FIG. 4. Overall manual reaction time: Lesion×Sex. Manual reaction time is averaged across visual field and cue validity. Open bar = normal subjects (N); light shade = left frontal subjects (LF); downward diagonal = right frontal subjects (RF); upward diagonal = right parietal subjects (RP). SEMs are indicated by vertical bars. X = manual reaction time for neutral condition averaged across visual field.

significant effect of lesion on overall reaction time described above was due to the performance of the right frontal females (n = 3) and the right parietal males (n = 3) (fig. 4). Overall, the right parietal males and right frontal females were slower than the normal subjects (*see* fig. 2, left side), whereas the right frontal males and right parietal females were no slower than the normal subjects (*see* fig. 2, right side). The averaged overall reaction times found for right frontal females and right parietal males (673 ms) was significantly different from the averaged reaction time for the remaining groups (541 ms) (critical difference = 41, actual difference = 132 ms). The overall reaction times of the right frontal males and right parietal females (averaged reaction time = 547 ms) did not differ significantly from those of the left frontal and normal subjects (averaged reaction time = 537 ms) (critical difference = 39, actual difference = 10 ms).

Analysis of a significant Lesion×Sex×Visual Field×Cue Validity interaction (F(6/64) = 2.27, $P < 0.05$) suggested that the right frontal males (n = 4) and right parietal females (n = 4), who showed no overall elevation in reaction times when compared with the normal subjects differed significantly from normal subjects in their ability to use the spatial cues (*see* fig. 2, right side). The right frontal males and right parietal females showed no significant effect of cue validity on reaction time. In an attempt to understand the contribution of the cue validity factor to this 4-way interaction, an analysis of the neutral cue alone was conducted. A significant effect of Lesion (F(3/32) = 2.98, $P < 0.05$) and Sex (F(1/32) = 5.58, $P < 0.05$) and a significant Lesion×Sex interaction (F(3/32) = 3.56, $P < 0.05$) were found in the neutral condition analysis. The specific relationships found in this analysis of neutral trials were identical to those found for overall manual reaction time. This concurrence between the neutral condition and overall reaction times is shown in fig. 4. The mean of the median reaction times for the neutral condition averaged across visual field is represented for each group by an 'X'. Similar to the normal subjects, the neurological subjects responded significantly faster to targets in either visual field following the valid cues than following the neutral or invalid cues. Although the responses for the invalid condition were slower than for the neutral condition, this difference was not significant. Perhaps reaction time was elevated in the neutral condition because the double arrow acted as an invalid cue by holding the subject's attention at fixation. Thus cue benefits were exaggerated and cue costs reduced.

With the elimination of neutral condition reaction times, the 4-way interaction found in the analysis of all subjects dropped out of the ANOVA results, leaving 2 significant interactions, a Lesion×Sex×Cue Validity interaction (F(2/28) = 3.55, $P < 0.05$) and a Lesion×Sex×Visual Field interaction (F(2/28) = 3.34, $P = 0.05$) when the right hemisphere (right frontal and parietal subjects) and normal subjects were compared (figs 5, 6). The left frontal subjects were excluded from the analysis at this point because no significant interactions involving both the visual field and cue validity factors, that would differ from the right frontal and parietal subjects, could be predicted for this group. Analysis including all subject groups therefore could obscure any relationships existing between the experimental factors and right hemispheric function. Assessment of the cue validity effect for each group revealed that the right frontal males and right parietal females were indistinguishable from normals in overall reaction time. Right frontal males and right parietal females were different from normal females, normal

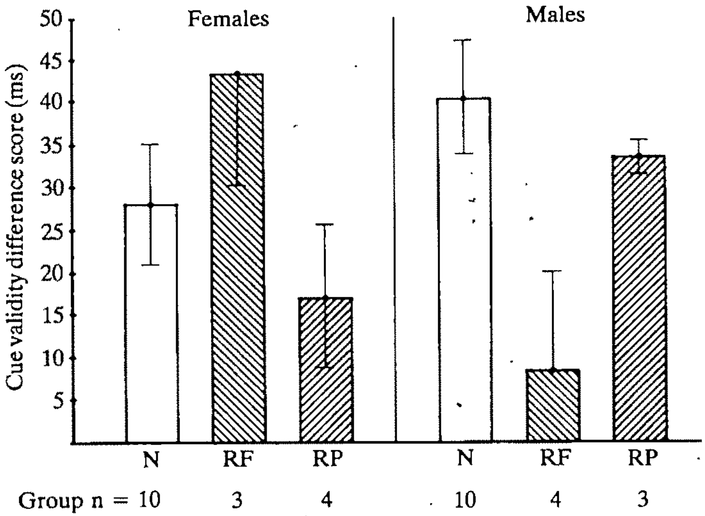


FIG. 5. Overall effect of cue validity on manual reaction time: Lesion×Sex. Cue validity effect is represented by manual reaction times following invalid cues averaged across visual field minus reaction times following valid cues averaged across visual field. Open bar = normal subjects (N); downward diagonal = right frontal subjects (RF); upward diagonal = right parietal subjects (RP). SEMs are indicated by a vertical bar.

males, right frontal females and right parietal males in their ability to use the cues (*see* fig. 2, right side). Fig. 5 shows these findings in terms of cue validity difference scores (reaction time for invalid cue condition minus reaction time for valid cue condition). The larger difference scores represent a greater effect of cue validity on reaction time. The right frontal males and right parietal females showed no effect of cue validity in either visual field. Their average cue validity difference score (12 ms) was significantly less than the average of the normal groups (34 ms) and from the average of right frontal females and right parietal males (38 ms). The right parietal females (17 ms) did not differ from the right frontal males (8 ms) in their lack of ability to use the cues (critical difference = 46 ms, actual difference = 9 ms). The right parietal males (33 ms) and right frontal females (43 ms) did not differ in their ability to use the cues effectively (critical difference = 40 ms, actual difference = 10 ms), and their averaged difference score (38 ms) did not differ from the averaged score (34 ms) for the normal groups (critical difference = 19 ms, actual difference = 4 ms). The corrected F ratio for the above Scheffé contrasts was 29.4.

Analysis of the significant Lesion×Sex×Visual Field interaction revealed some interesting relationships. Fig. 6 shows these results in terms of visual field difference scores (reaction time to left visual field targets minus reaction time to right visual field targets). A score with a larger absolute value represents a greater visual field difference. Positive scores reflect slower reaction times for the left visual field, whereas negative scores indicate slower reaction times for the right visual field. The right parietal females and right frontal males responded with equal speed to targets appearing in either visual field. The right parietal females (4 ms) and right frontal males (1 ms) did not differ

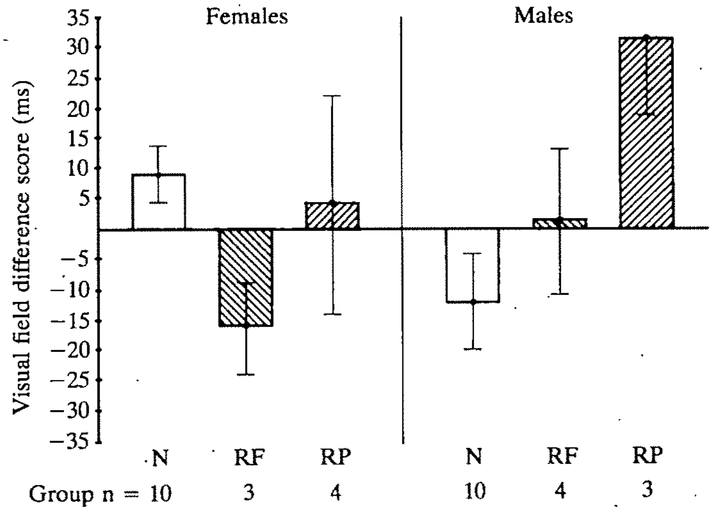


FIG. 6. Overall effect of visual field on manual reaction time: Lesion×Sex. Visual field effect is represented by manual reaction times to left visual field target averaged across cue validity minus reaction times to right visual field target averaged across cue validity. Positive scores represent slower reaction times to left visual field target, negative scores represent slower reaction times to right visual field target. Open bar = normal subjects (N); downward diagonal = right frontal subjects (RF); upward diagonal = right parietal subjects (RP). SEMs are indicated by a vertical bar.

in this lack of a visual field difference in reaction time (critical difference = 33 ms, actual difference = 3 ms). These are the same groups that showed a significant bilateral reduction in cue validity effect. All other groups showed a significant visual field effect on overall reaction time (normal females, normal males, right frontal females and right parietal males). However, there were group differences in the visual field associated with the elevated manual reaction times (*see* fig. 2, left side). Normal females and right parietal males responded more slowly to the target in the left visual field than in the right (*see* fig. 2, upper left). The average of their visual field difference scores (20 ms) was significantly different from the normal male and right frontal female averaged difference score (−14 ms) based on a critical difference of 22 ms. The normal males and right frontal females responded more slowly to the target appearing in the right visual field than the left visual field (*see* fig. 2, lower left). The groups with positive visual field difference scores did not differ from each other (critical difference = 32 ms, actual difference = 22 ms), and the groups with negative scores did not differ from each other (critical difference = 32 ms, actual difference = 4 ms).

Since no visual field difference was found for the lack of cue validity effect shown in fig. 5, a test was performed to see if a patient's anticonvulsant drug dosage was related to overall effect of cue validity. Rank-ordered medication dosage was not significantly correlated with rank-ordered overall cue validity difference scores (Spearman rho = −0.18, t = 0.63, df = 12, $P > 0.5$). However, the data available are insufficient to eliminate this variable as a possible confounding factor.

TABLE 3. MEDIAN SACCADE REACTION TIMES (ms) FOR VALID, NEUTRAL AND INVALID CUE TRIALS: NORMAL SUBJECTS

	Left visual field			*Right visual field*		
	Valid	*Neutral*	*Invalid*	*Valid*	*Neutral*	*Invalid*
Female						
NF1	218	265	255	231	284	292
NF2	217	253	275	259	290	290
NF3	200	228	257	209	219	227
NF4	193	239	240	181	244	258
NF5	158	221	246	150	264	274
NF6	217	265	270	226	278	271
NF7	179	214	233	178	212	226
NF8	238	293	301	173	218	220
NF9	237	277	247	257	299	286
NF10	206	241	251	192	214	230
Mean	*206*	*250*	*258*	*206*	*252*	*257*
SD	*25*	*26*	*20*	*37*	*35*	*29*
Male						
NM1	198	240	227	207	256	239
NM2	208	244	256	193	228	238
NM3	175	196	248	171	247	249
NM4	170	207	186	196	247	209
NM5	236	278	297	245	313	350
NM6	218	263	288	206	267	259
NM7	186	223	222	196	217	257
NM8	177	268	314	197	266	324
NM9	306	320	325	359	365	420
NM10	249	261	269	262	268	266
Mean	*212*	*250*	*263*	*223*	*267*	*281*
SD	*42*	*36*	*44*	*55*	*43*	*64*
Overall						
Mean	*209*	*250*	*260*	*214*	*260*	*269*
SD	*34*	*31*	*33*	*46*	*39*	*50*

Experiment 2

Saccade reaction time

The saccade reaction time data of the normal subjects are shown in Table 3. Analysis of these data indicated a highly significant overall effect of cue validity (F(2,36) = 57.44, $P < 0.01$) with males (n = 10) and females (n = 10) being equal on this measure. The reaction times to targets following a valid cue were significantly faster than reaction times following a neutral or invalid cue. There was a nonsignificant trend for the reaction times in the invalid condition to be slower than in the neutral condition. Because of a lack of difference between neutral and invalid cues, the cue validity factor was further analysed using only the valid and invalid cue conditions.

When the neurological subjects (Table 4) were added to the analysis, there was an overall significant main effect of cue validity (valid vs invalid: F(1,32) = 92.28, $P < 0.01$). Their performance was indistinguishable from the normal subjects' performance.

A significant Sex × Visual Field × Cue Validity interaction was found (F(1,27) = 8.22,

TABLE 4. MEDIAN SACCADE REACTION TIMES (ms) FOR VALID, NEUTRAL AND INVALID CUE TRIALS: NEUROLOGICAL SUBJECTS

	Left visual field			*Right visual field*		
	Valid	*Neutral*	*Invalid*	*Valid*	*Neutral*	*Invalid*
Female: left frontal						
LF1	235	243	291	241	276	284
LF2	197	246	254	202	205	217
Mean	*216*	*245*	*273*	*222*	*241*	*251*
SD	*27*	*2*	*26*	*28*	*50*	*47*
Male: left frontal						
LF3	272	306	305	297	385	379
LF4	161	187	169	176	189	203
LF5	206	244	245	172	182	223
LF6	144	174	163	144	150	153
Mean	*196*	*228*	*221*	*197*	*227*	*240*
SD	*57*	*60*	*68*	*68*	*107*	*98*
Overall Mean	*203*	*233*	*238*	*205*	*231*	*243*
Overall SD	*47*	*48*	*60*	*56*	*86*	*79*
Female: right frontal						
RF1	195	228	261	197	219	257
RF2	241	254	313	318	329	364
RF3	310	328	377	274	275	305
Mean	*249*	*270*	*317*	*263*	*274*	*309*
SD	*58*	*52*	*58*	*61*	*55*	*54*
Male: right frontal						
RF4	210	267	280	206	365	287
RF5	220	216	243	243	262	298
RF6	181	250	211	167	197	179
RF7	220	259	277	248	319	310
Mean	*208*	*248*	*253*	*216*	*286*	*269*
SD	*18*	*22*	*33*	*38*	*73*	*60*
Overall Mean	*225*	*257*	*280*	*236*	*281*	*286*
Overall SD	*42*	*36*	*53*	*51*	*61*	*57*
Female: right parietal						
RP1	202	204	223	194	201	198
RP2	236	290	224	207	219	220
RP3	188	218	260	150	137	158
RP4	203	220	217	208	233	231
Mean	*207*	*233*	*231*	*190*	*198*	*202*
SD	*20*	*39*	*20*	*27*	*42*	*32*
Male: right parietal						
RP5	202	291	239	146	162	193
RP6	206	244	246	230	260	273
RP7	296	307	357	276	316	321
Mean	*235*	*281*	*281*	*217*	*246*	*262*
SD	*53*	*33*	*66*	*66*	*78*	*65*
Overall Mean	*219*	*253*	*252*	*202*	*218*	*228*
Overall SD	*37*	*42*	*49*	*45*	*60*	*54*

$P < 0.01$). Fig. 7 shows the results for the analysis of valid and invalid trial data for all subjects. Data are represented by visual field difference scores ((reaction time for invalid condition left visual field minus valid condition left visual field) minus (reaction time for invalid condition right visual field minus valid condition right visual field)). It was found that females showed a greater effect of cue validity in the left visual field

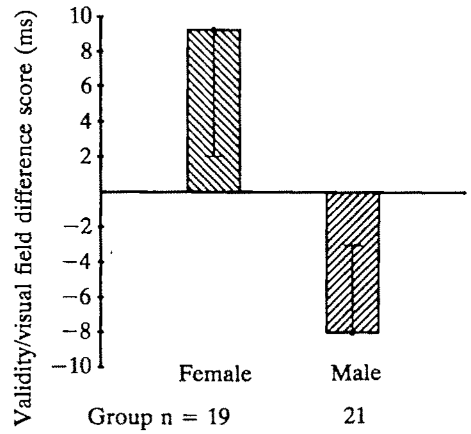


FIG. 7. Visual field difference in cue validity effect on saccade reaction time: Sex differences. Cue validity effect is represented by cue validity effect in the left visual field minus right visual field. Positive scores represent a greater cue validity effect in the left visual field, negative scores a greater effect in the right visual field. Downward diagonal = female subjects; upward diagonal = male subjects. SEMs are indicated by vertical bars.

than the right visual field, while males showed a greater effect of cue validity in the right visual field than the left visual field (*see* fig. 2, top and bottom). The female visual field difference score of 9 ms differed significantly from the male visual field difference score of −9 ms. The critical difference of 7 ms calculated for this contrast was smaller than the actual difference between the means (18 ms).

Saccade amplitude

Saccade amplitude was measured to assess the effects of cortical damage on the functioning of the saccade-generating system while performing a task of directed visual attention. Analysis of the normal subjects' saccade amplitude (Table 5) revealed no significant effect of cue validity, visual field or sex. However, significant differences were found when the neurological subjects (Table 6) were added to the analysis.

As was the case for Experiment 1, the clearest findings apply to the right hemisphere groups. The following results are reported for an analysis that excluded the left frontal subjects. The performance of the left frontal subjects will be discussed at the end of this section.

A significant Group×Cue Validity interaction was found (F(2,28) = 3.80, $P < 0.05$) in the analysis of the right hemisphere groups. The normal subjects were not significantly affected by cue validity. However, right frontal (n = 7) and right parietal (n = 7) lesions had a different effect on saccade amplitude. The right frontal subjects made larger saccades to the target following the invalid cues than the valid cues, while the right parietal subjects made larger saccades to the target following the valid cues than the invalid cues. This difference was significant (critical difference = 0.36°, actual difference = 0.91°). The right frontal subjects' difference score (0.35°) differed significantly from the normal subjects' difference score (−0.02°) (critical difference = 0.33°, actual difference =

TABLE 5. MEAN SACCADE AMPLITUDES (DEGREE OF VISUAL ANGLE) FOR VALID, NEUTRAL AND INVALID CUE TRIALS: NORMAL SUBJECTS

	Left visual field			*Right visual field*		
	Valid	*Neutral*	*Invalid*	*Valid*	*Neutral*	*Invalid*
Female						
NF1	10.0	9.9	10.2	10.4	10.4	10.4
NF2	10.7	11.7	11.0	10.4	12.0	11.4
NF3	9.8	10.0	10.1	9.6	9.6	9.6
NF4	9.7	10.0	10.2	9.2	9.5	9.5
NF5	7.7	8.7	6.8	8.1	8.6	9.1
NF6	10.3	10.5	10.1	10.1	10.0	9.2
NF7	8.8	9.6	9.9	7.7	7.8	6.5
NF8	9.5	10.2	10.4	8.8	9.6	9.7
NF9	8.7	8.2	8.4	9.6	8.3	9.3
NF10	10.2	10.7	10.3	10.4	10.4	10.5
Mean	*9.5*	*10.0*	*9.7*	*9.4*	*9.6*	*9.5*
SD	*0.9*	*1.0*	*1.2*	*1.0*	*1.2*	*1.3*
Male						
NM1	9.4	9.6	10.0	10.0	10.3	10.4
NM2	10.4	10.3	9.1	11.4	12.1	11.9
NM3	9.3	9.5	8.9	9.0	10.0	8.8
NM4	8.3	8.5	7.4	7.6	7.5	6.7
NM5	9.4	9.5	9.2	9.8	9.5	10.1
NM6	10.1	11.0	10.7	11.3	10.9	9.8
NM7	10.1	9.8	9.9	9.7	9.6	10.5
NM8	9.5	8.9	9.0	10.1	10.4	9.9
NM9	8.6	8.4	9.0	8.5	8.8	8.6
NM10	9.7	9.6	9.0	9.4	9.6	9.0
Mean	*9.5*	*9.5*	*9.2*	*9.7*	*9.9*	*9.6*
SD	*0.7*	*0.8*	*0.9*	*1.2*	*1.2*	*1.4*
Overall						
Mean	*9.5*	*9.7*	*9.5*	*9.6*	*9.7*	*9.5*
SD	*0.8*	*0.9*	*1.1*	*1.1*	*1.2*	*1.3*

0.37°). The right parietal subjects (−0.56°) also differed significantly from the normal subjects (critical difference = 0.33°, actual difference = 0.54°).

Analysis of a significant Group × Visual Field × Cue Validity interaction (F(2,28) = 3.30, $P = 0.05$) revealed that cue validity affected only those saccades made to the left visual field targets, contralateral to the subjects' right hemisphere damage (fig. 8). The positive difference scores represent larger saccades following the invalid cues, while the negative scores represent larger saccades following the valid cues. The normal subjects showed no interaction between visual field and cue validity. The right frontal and right parietal subjects showed an effect of cue validity that was restricted to the left visual field. The right frontal subjects made larger saccades to the left visual field target following the invalid cues, while the right parietal subjects made larger saccades to the left visual field following the valid cues. However, neither of the neurological groups showed an effect of cue validity in the right visual field. The averaged right visual field difference scores of the right frontal and right parietal subjects (−0.04°) did not differ significantly from the right visual field difference score of −0.01° found for the normal subjects (critical difference = 0.43°, actual difference = −0.03°). However, when the left visual

TABLE 6. MEAN SACCADE AMPLITUDES (DEGREE OF VISUAL ANGLE) FOR VALID, NEUTRAL AND INVALID CUE TRIALS: NEUROLOGICAL SUBJECTS

	Left visual field			*Right visual field*		
	Valid	*Neutral*	*Invalid*	*Valid*	*Neutral*	*Invalid*
Female: left frontal						
LF1	10.0	10.1	10.7	10.7	10.6	10.4
LF2	7.0	8.6	8.5	8.5	7.7	6.7
Mean	*8.5*	*9.4*	*9.6*	*9.6*	*9.2*	*8.6*
SD	*2.1*	*1.1*	*1.6*	*1.6*	*2.1*	*2.6*
Male: left frontal						
LF3	9.6	9.5	9.9	9.7	9.7	9.8
LF4	9.3	9.6	9.1	8.8	8.9	8.7
LF5	9.6	9.5	9.7	9.8	9.4	10.0
LF6	9.7	9.3	9.6	8.4	9.3	8.5
Mean	*9.5*	*9.5*	*9.6*	*9.2*	*9.3*	*9.3*
SD	*0.2*	*0.1*	*0.3*	*0.7*	*0.3*	*0.8*
Overall Mean	*9.2*	*9.4*	*9.6*	*9.3*	*9.3*	*9.0*
Overall SD	*1.1*	*0.5*	*0.7*	*0.9*	*1.0*	*1.4*
Female: right frontal						
RF1	8.6	7.8	10.0	8.8	8.5	9.4
RF2	9.1	10.9	8.8	8.6	8.4	8.2
RF3	8.2	7.8	8.3	9.4	9.4	8.2
Mean	*8.6*	*8.8*	*9.0*	*8.9*	*8.8*	*8.6*
SD	*0.5*	*1.8*	*0.9*	*0.4*	*0.6*	*0.7*
Male: right frontal						
RF4	12.3	12.2	13.4	10.4	10.7	11.3
RF5	10.0	9.7	10.3	10.2	10.0	10.3
RF6	8.6	9.9	8.1	8.1	8.3	8.1
RF7	8.5	9.4	10.2	8.3	9.2	8.5
Mean	*9.9*	*10.3*	*10.7*	*9.3*	*9.6*	*9.6*
SD	*1.8*	*1.3*	*1.9*	*1.2*	*1.0*	*1.5*
Overall Mean	*9.3*	*9.7*	*10.0*	*9.1*	*9.2*	*9.1*
Overall SD	*1.4*	*1.6*	*1.7*	*0.9*	*0.9*	*1.2*
Female: right parietal						
RP1	9.7	9.3	8.7	11.2	9.3	10.7
RP2	9.5	9.9	7.9	8.5	8.2	7.9
RP3	8.8	6.9	6.4	7.9	8.4	7.8
RP4	11.5	11.8	10.7	10.2	11.0	10.8
Mean	*9.9*	*9.5*	*8.4*	*9.5*	*9.5*	*9.3*
SD	*1.2*	*2.0*	*1.8*	*1.5*	*1.4*	*1.7*
Male: right parietal						
RP5	8.4	8.6	7.0	9.1	9.4	9.1
RP6	11.3	11.2	12.2	10.8	10.1	10.9
RP7	9.9	10.0	10.3	9.9	10.3	9.7
Mean	*9.9*	*9.9*	*9.8*	*9.9*	*9.9*	*9.9*
SD	*1.5*	*1.3*	*2.6*	*0.9*	*1.2*	*1.3*
Overall Mean	*9.9*	*9.7*	*9.0*	*9.7*	*9.7*	*9.6*
Overall SD	*1.2*	*1.6*	*2.1*	*1.2*	*1.1*	*1.3*

field difference scores were compared it was found that the right frontal and right parietal subjects differed significantly from the normal subjects. The critical difference for both of these contrasts was 0.43°. The actual difference between the amplitude difference scores found for the right frontal and normal subjects was 0.70°. The actual difference between the amplitude difference scores found for the right parietal and normal subjects

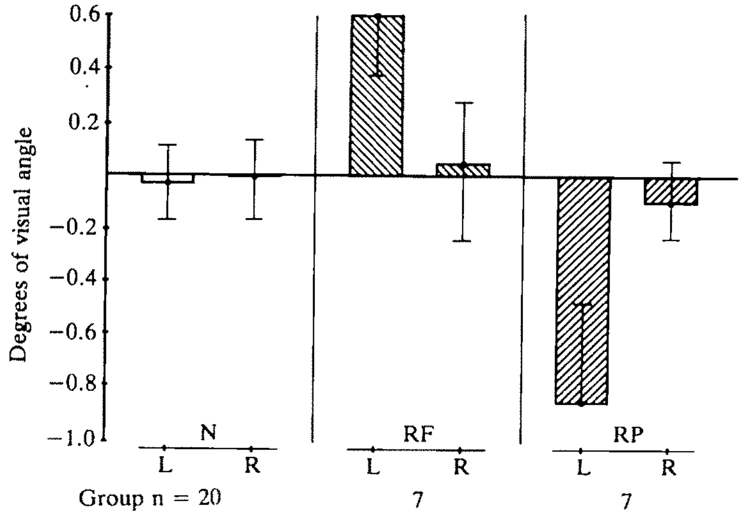


FIG. 8. Effect of cue validity on saccade amplitude: Lesion × Visual Field. Cue validity effect is represented by amplitude for the invalid condition minus that for the valid condition. Positive scores represent larger saccades to the target following invalid cues, negative scores larger saccades following valid cues. Open bar = normal subjects (N); downward diagonal = right frontal subjects (RF); upward diagonal = right parietal subjects (RP). Left bar for each group represents score for the left visual field (L), right bar for each group represents score for the right visual field (R). SEMs are indicated by a vertical bar.

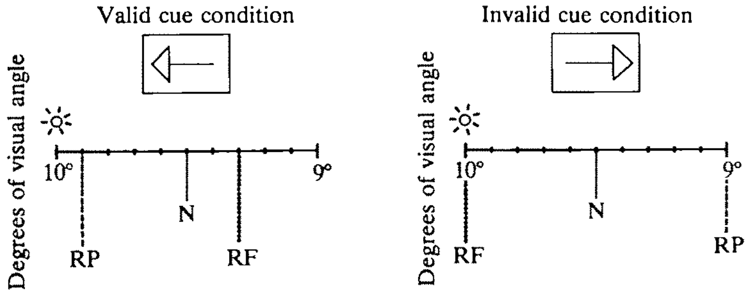


FIG. 9. Cue validity effect on saccade amplitude to left visual field targets. Normal subjects (N) consistently undershot the target but showed no effect of cue validity. Compared with the normal subjects, the right frontal subjects (RF) made hypometric saccades to the target following the valid cues. The right parietal (RP) subjects made hypermetric saccades to the target following the valid cues and hypometric saccades following the invalid cues.

was 0.83°. Furthermore, the left visual field difference scores found for the right frontal and right parietal subjects (0.67° and −0.86°, respectively) were significantly different (critical difference = 0.46°, actual difference = 1.53°).

The mean amplitude of saccades to the left visual field target following the valid and invalid cues is shown in fig. 9. From this perspective it can be seen that when compared with the normal subjects, the saccades made by right frontal subjects were consistently hypometric following the valid cues and hypermetric following the invalid cues. The performance of the right parietal group was opposite to that of subjects in the right frontal group. The latter subjects made hypermetric saccades to the target following the valid cues and hypometric saccades to the target following the invalid cues. It is unclear why the normal subjects consistently undershot the target to the degree shown by the data. Perhaps fatigue (Bahill and Stark, 1975) and the predictable saccade size increased a normal tendency for glissadic undershooting (Becker and Fuchs, 1969; Troost *et al.*, 1974; Bahill and Troost, 1979).

The final significant result in the data for the right hemisphere, saccade amplitude analysis was a Group×Sex×Cue Validity interaction (F(2,28) = 4.06, $P < 0.05$). It indicated that the above right frontal overall cue validity effect was due primarily to the performance of the male subjects in that group (n = 4), while the right parietal effect described above was due to the female subjects in that group (n = 4) (*see* fig. 2, right side). This result is shown in fig. 10 by cue validity difference scores (saccade amplitude for invalid condition averaged across visual field minus saccade amplitude for valid condition averaged across visual field). A positive score represents larger saccades to targets following the invalid cues, while a negative score represents larger saccades to targets following the valid cues. Both female and male normal subjects were unaffected significantly by the cues, although there was a slight trend ($P = 0.10$) in the data suggesting that normal females and males were affected in an opposing manner by the cue validity factor. The right parietal males and the right frontal females were unaffected significantly by the cues in this measure. However, the right frontal males

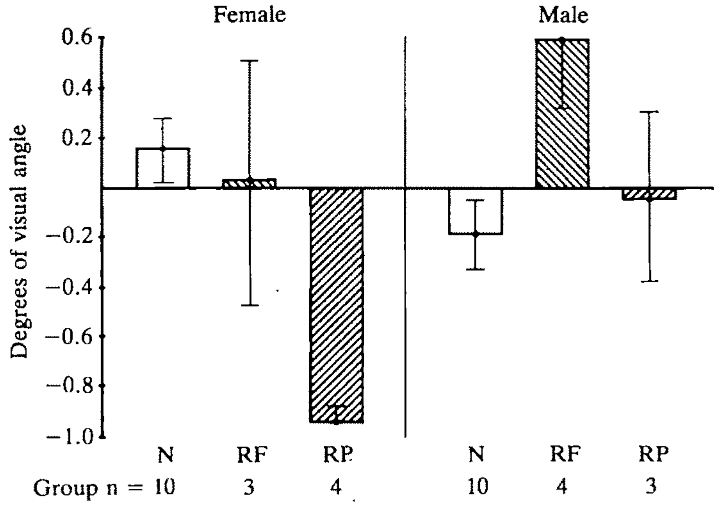


FIG. 10. Effect of cue validity on saccade amplitude: Lesion×Sex. Cue validity effect is represented by amplitude for the invalid cue condition minus that for the valid cue condition. Positive scores represent larger saccades to the target following invalid cues, negative scores larger saccades to the target following valid cues. Open bar = normal subjects (N); downward diagonal = right frontal subjects (RF); upward diagonal = right parietal subjects (RP). SEMs are indicated by vertical bars.

and the right parietal females were significantly affected by cue validity. The averaged difference scores found for the right frontal females and right parietal males (−0.01°) was indistinguishable from the averaged difference score of −0.02° found for the normal females and males (critical difference = 0.64°, actual difference = −0.01°). Furthermore, the right frontal females (0.03°) and right parietal males (−0.05°) did not differ significantly (critical difference = 0.83°, actual difference = 0.08°). In contrast, the right frontal males (0.59°) differed significantly from the normal subjects (−0.02°) (critical difference = 0.57°, actual difference = 0.61°) and the right parietal females (−0.95°) differed significantly from the normal subjects (−0.02°) (critical difference = 0.57°, actual difference = 0.93°). In addition, the right frontal males and right parietal females differed significantly (critical difference = 0.72°, actual difference = 1.54°). The contrast between right parietal females and right parietal males was significant (critical difference = 0.77°, actual difference = 1.0°). However, the contrast between right frontal males and right frontal females was not significant (critical difference = 0.77°, actual difference = 0.62°). One female (RF2) showed the same effect as that found for the right frontal male subjects.

The ANOVA for all subjects (including the left frontal group) revealed a significant Group×Sex×Visual Field×Cue Validity interaction ($F(3,32) = 3.42$, $P < 0.05$). Analysis of this 4-way interaction suggested that the significant visual field effect shown in fig. 8 could be attributed directly to the performance of the right frontal males and right parietal females. Thus the abnormal effect of cue validity found for these subjects may have been significantly greater for the left visual field.

The performance of the left frontal females and left frontal males is also of interest. The left frontal females were significantly affected by cue validity in both the left and right visual fields. However, the left frontal males like the normal subjects, the right frontal females and the right parietal males were unaffected by cue validity. The left frontal females overshot the target stimuli in the left visual field following the invalid cues, whereas they undershot the target stimuli in the right visual field following the invalid cues. Although both left frontal female subjects showed this pattern, the small number of subjects in this group requires that caution be used when interpreting these results.

Saccade duration

As would be expected, saccade duration was proportional to saccade amplitude (Leigh and Zee, 1983). Analysis of this relationship revealed the following significant interactions: Group×Cue Validity ($F(6,64) = 2.91$, $P < 0.05$), Group×Visual Field×Cue Validity ($F(6,64) = 2.42$, $P < 0.05$) and Group×Sex×Visual Field×Cue Validity ($F(6,64) = 4.20$, $P < 0.01$).

Saccade peak velocity

All analyses performed on these data indicated a significant main effect of visual field. This was true for the analysis of all subjects ($F(1,32) = 14.73$, $P < 0.01$) and normal subjects alone ($F(1,18) = 5.77$, $P < 0.05$). All subjects in this study showed a higher saccadic peak velocity when they looked into the left visual field (overall mean = 647 deg/s, SEM = 7) than when they looked into the right visual field (overall mean = 609 deg/s, SEM = 4). This phenomenon does not appear to have been reported previously. It may be important that the absolute peak velocity values found in the present study were large relative to values reported previously for 10° saccades (Boghen *et al.*, 1974). In their study, Boghen *et al.* demonstrated that a recording system using higher bandwidths yielded faster and more accurate velocities. Perhaps the large overall peak velocity values and visual field differences found in the present study were due to the bandwidth and the fast sampling rate of 1,000 Hz used (chosen in order to increase the accuracy of the reaction time variable). The faster sampling rate used could have increased the effect of noise on the data. However, an increase in sensitivity to noise does not provide a good explanation for the visual field differences.

A previous study of the saccadic eye movement system showed that hemidecortication resulted in lower peak velocities and longer durations of saccades to either visual field (Sharpe *et al.*, 1979). It is unclear why this effect was not found in patients with more restricted cortical lesions. Perhaps large cortical lesions are necessary before cortical modulation of brainstem saccade centres is affected. The subjects in the Sharpe study underwent hemidecortication at an early age; 3 of the 5 subjects were under 6 months of age at the time of surgery. Perhaps differences in neural development account for the discrepancy. The lack of a cue validity effect suggests that changes in directed visual attention have little to do with the speed of orienting saccades.

Lesions analyses

Computerized tomographic brain scans were analysed for each subject. A technique described by Mazzocchi and Vignolo (1978) was used to verify the angle of the templates. Representative drawings of each lesion were made on standard templates (Damasio, 1983; figs 11 – 13). Lesion volume was determined by computer digitization of the area of lesion at each scan level. Each lesion was characterized according to total volume of damaged neural tissue, as well as volume of the lesion in superior frontal lobe, inferior frontal lobe, superior parietal lobe, inferior parietal lobe, occipital lobe, limbic lobe (cingulate gyrus), temporal lobe and subcortex as defined in Damasio (1983). These data (Tables 7 and 8) were analysed to assess the possibility that the lesion site by sex interactions were due to differences in lesion site. The result of this analysis was negative. To address the possibility that the behavioural results were due to overall size of lesion rather than lesion site, the neurological subjects were assigned to one of three groups depending on the extent of their lesion (Tables 7 and 8). All analyses reported above were performed using the three total lesion size groups in place of the lesion site groups. It was determined that total lesion size had no main or interactive effect on any of the saccade-dependent variables.

Subject variables

Each subject was assessed for values of some neurological (Table 9) and some psychometric and demographic variables (Table 10) at the time of experimental testing.

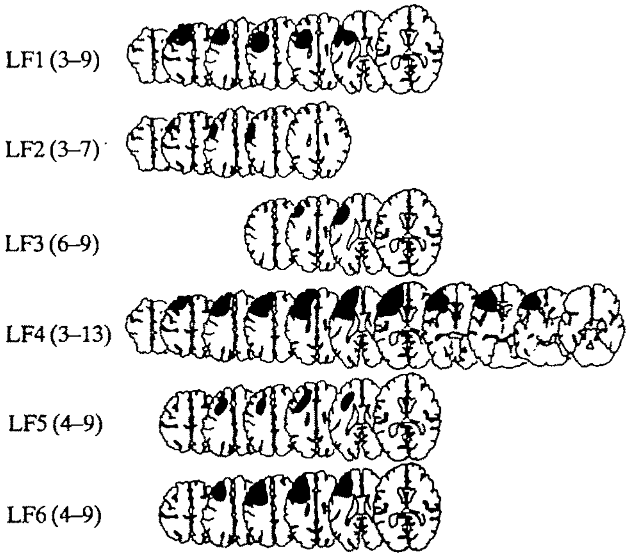


FIG. 11. Representative diagrams of cerebral damage based on CT scans: left frontal subjects. Black areas indicate regions of damage, affected section numbers in brackets.

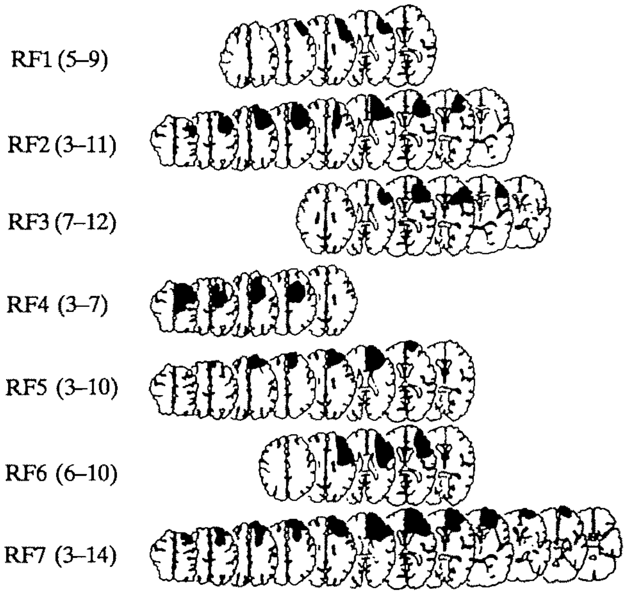


FIG. 12. Representative diagrams of cerebral damage based on CT scans: right frontal subjects. Black areas indicate regions of damage, affected section numbers in brackets.

Each of these variables was subjected to a one-way analysis of variance to test for the significant group differences. Additional analyses were performed when significant group differences were found.

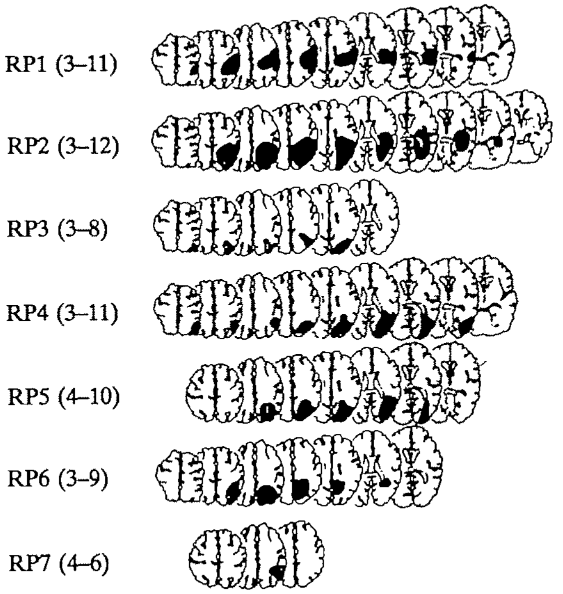


FIG. 13. Representative diagrams of cerebral damage based on CT scans: right parietal subjects. Black areas indicate regions of damage, affected section numbers in brackets.

When the aetiology of the lesions (*see* Table 7) was used to group the data, it was found that aetiology had no main or interactive effect on manual reaction time, saccade reaction time, duration or peak velocity. However, aetiology did have a significant main effect on saccade amplitude (F(3,14) = 4.91, $P < 0.05$). Subjects with cerebral abscess or haemorrhage from an arteriovenous malformation tended to make larger saccades (mean saccade amplitude = 10.2° and 10.9°, respectively), than subjects with depressed skull fracture, vascular infarction or astrocytoma (mean saccade amplitude = 9.0°, 8.9° and 9.0°, respectively). The data were analysed to see if this finding could be explained in terms of sex, lesion site, total lesion size or medication, with negative results. Aetiology did not interact with the other experimental factors. Therefore, aetiology was not responsible for the significant lesion group, visual field or cue validity effects found in the saccade amplitude data.

The patients were assigned to one of two groups depending on the time from the onset of their neurological damage: 4–12 mos vs greater than 12 mos. This variable, when used as a grouping factor in place of lesion site, had no main or interactive effect on any of the saccade dependent variables.

An estimate of premorbid IQ, used as an index of socioeconomic level (Wilson *et al.*, 1979), distinguished some of the subject groups in an analysis of variance. Right frontal females had significantly lower IQ scores than the other groups and right parietal males had significantly higher IQ scores than the other groups. Therefore, the estimated IQ score was used as a covariate in the analysis of variance tests reported earlier. This covariate had no systematic effect on or relationship with the other experimental factors.

TABLE 7. PERCENTAGE OF DAMAGED TISSUE WITHIN CEREBRAL REGIONS AFFECTED BY NEUROLOGICAL DISEASE: LEFT AND RIGHT FRONTAL PATIENTS

	Superior frontal lobe[a]	*Inferior frontal lobe*[b]	*Total frontal lobe*	*Parietal lobe*	*Limbic lobe*	*Subcortex*	*Total lesion size*[c]	*Total lesion size group*[d]
Left frontal								
Females								
LF1	22	0	22	3	0	4	9	2
LF2	3	0	3	1	0	0	1	1
Mean	*13*	*0*	*13*	*2*	*0*	*2*	*5*	
Males								
LF3	6	0	6	0	0	0	2	1
LF4	9	0	9	1	0	2	3	3
LF5	21	0	21	0	4	0	7	1
LF6	64	36	50	6	7	0	19	2
Mean	*25*	*9*	*22*	*2*	*3*	*0.5*	*8*	
Right frontal								
Females								
RF1	9	0	9	1	0	0	3	1
RF2	52	14	33	4	4	1	12	3
RF3	5	22	14	2	0	3	5	1
Mean	*22*	*12*	*19*	*2*	*1*	*1*	*7*	
Males								
RF4	41	0	20	5	7	0	9	2
RF5	32	4	18	0	5	0	6	1
RF6	14	12	13	8	0	3	7	2
RF7	60	20	40	3	19	0	16	3
Mean	*37*	*9*	*23*	*4*	*8*	*1*	*10*	

[a] Region corresponding roughly to Brodmann's areas 4, 6, 8, superior 9 and superior 32.

[b] Region corresponding roughly to Brodmann's areas inferior 9, inferior 32, 10, 11, 44, 45 and 46.

[c] Based on extent of total lesion found within area corresponding to sections 25°, 3–14.

[d] Group 1 = 1–6% total damage; Group 2 = 7–9% total damage; Group 3 = 10–19% total damage.

The main effect of estimated IQ was therefore insignificant and none of the significant results reported earlier were altered by the addition of the covariate.

DISCUSSION

Experiment 1—manual response

Overall, the normal females responded more slowly than the normal males. They also responded more slowly and showed a greater effect of cue validity to stimuli appearing in their left visual field than in their right visual field, whereas the normal males responded more slowly and showed a greater effect of cue validity to stimuli in their right visual field than in their left visual field (fig. 2, top and bottom). Previous studies on normal subjects, typically undergraduate students, using the same basic paradigm have not reported sex differences (Posner, 1978), although sex differences in this direction have been reported in other kinds of studies (Kimura, 1969; Rizzolatti and Buchtel, 1977; Heister, 1984). A study of 16 undergraduate students (8 of each sex, mean age = 19 yrs) was conducted using the same paradigm as used in the present study (Nagel-Leiby and Buchtel, unpublished data). An analysis of variance of these

TABLE 8. PERCENTAGE OF DAMAGED TISSUE WITHIN CEREBRAL REGIONS AFFECTED BY NEUROLOGICAL DISEASE: RIGHT PARIETAL PATIENTS

	Superior parietal lobe[a]	*Inferior parietal lobe*[b]	*Total parietal lobe*	*Occipital lobe*	*Temporal lobe*	*Limbic lobe*	*Subcortex*	*Total lesion size*[c]	*Total lesion size group*[d]
Right parietal									
Females									
RP1	36	0	27	0	20	0	0.5	10	3
RP2	46	9	38	39	14	7	18	19	3
RP3	7	0	9	9	0	0	0	3	1
RP4	10	18	10	53	2	0	0	9	2
Mean	*25*	*7*	*21*	*25*	*9*	*2*	*5*	*10*	
Males									
RP5	7	3	6	62	0	0	0	8	2
RP6	18	0	14	26	0	0	0	7	2
RP7	5	0	4	0	0	0	0	1	1
Mean	*10*	*1*	*8*	*29*	*0*	*0*	*0*	*5*	

[a] Region corresponding roughly to Brodmann's areas 5, 7, 39 and superior 40. CT scan sections 25°, 3–8.
[b] Region corresponding roughly to Brodmann's areas 3, 1, 2, 21, 37 and inferior 40. CT scan sections 25°, 9–11.
[c] Based on extent of total lesion found within area corresponding to CT scan sections 25°, 3–14.
[d] Group 1 = 1–6% total damage; Group 2 = 7–9% total damage; Group 3 = 10–19% total damage.

TABLE 9. CLINICAL DATA ON NEUROLOGICAL SUBJECTS

Case	*Sex*	*Age (yrs)*	*Aetiology*[a]	*Age of lesion (mos postonset)*	*Anticonvulsant drugs*[b,c]
			LEFT FRONTAL		
LF1	F	49	A	72	Ph(300/8.5)
LF2	F	23	I	6	–
LF3	M	44	I	4	–
LF4	M	40	A	12	–
LF5	M	30	I	5	–
LF6	M	28	F	4	–
			RIGHT FRONTAL		
RF1	F	47	F	4	P(60 mg) Ph(200/12/4)
RF2	F	36	I	12	–
RF3	F	29	T	72	P(30/15.4), V(250,45.9)
RF4	M	34	H	8	P(120/22/5) Ph(300/17.6), D-5 mg,
RF5	M	25	T	16	C(900 mg), Ph(250/14.5)
RF6	M	57	I	12	–
RF7	M	40	T	60	P(80/23.1) Ph(500/7.6)
			RIGHT PARIETAL		
RP1	F	25	H	24	Ph(100/10.6)
RP2	F	21	T	7	Ph(200/13.2)
RP3	F	17	I	72[d]	–
RP4	F	24	H	12	–
RP5	M	27	T	12	Ph(400/14.7), P(135/35.0)
RP6	M	41	A	14	P(120/13.6)
RP7	M	33	I	5	–

[a] A = abscess; F = depressed skull fracture; H = haemorrhage from arteriovenous malformation; I = vascular infarct; T = astrocytoma. [b] C = carbamazepine (Tegretol); D = diazepam; P = phenobarbital; Ph = phenytoin; V = velproic acid. [c] (dose in mg/serum level in μg/ml). [d] Onset uncertain, possible birth trauma.

TABLE 10. DESCRIPTIVE STATISTICS FOR DEMOGRAPHIC AND PSYCHOMETRIC VARIABLES

	Normal		*L frontal*		*R frontal*		*R parietal*	
	Female	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*
Age								
Mean	34.9	39.8	36.0	35.5	37.3	39.2	22.2	33.6
SD	9.9	11.6	18.3	7.7	9.1	13.5	3.6	7.0
$F = 1.29$, $df = 7/32$, $P = 0.28$								
Predicted IQ[a]								
Mean	104.2	105.8	102.0	101.7	91.6	105.7	98.8	114.6
SD	5.8	8.5	7.1	5.4	0.6	6.9	4.6	6.6
$F = 3.21$, $df = 7/32$, $P = 0.01$								
Hand preference								
Mean	21.6	24.4	23.0	23.3	21.0	25.2	34.8	32.3
SD	4.7	8.0	7.1	4.6	2.6	4.6	15.4	16.4
$F = 1.49$, $df = 7/32$, $P = 0.20$								
Visual field scan[b]								
Mean	33.9	39.1	66.5	42.7	64.3	58.5	47.0	137.6
SD	4.4	8.5	27.6	6.8	35.3	30.8	10.6	169.2
$F = 2.00$, $df = 7/32$, $P = 0.08$								
Symbol-digit written								
Mean	55.1	51.6	30.5	42.8	39.0	39.5	48.5	41.7
SD	8.6	7.1	6.4	7.9	8.7	7.3	15.9	14.9
$F = 3.18$, $df = 7/32$, $P = 0.01$								
Symbol-digit oral								
Mean	64.1	59.2	31.5	52.5	43.0	36.3	55.8	47.3
SD	8.0	13.0	6.4	15.2	12.6	5.4	17.7	18.5
$F = 3.84$, $df = 7/32$, $P = 0.003$								

[a] Based on age, sex, education and occupation. [b] Scan time in seconds.

data revealed a main effect of cue validity (F = 29.40, $P < 0.001$). The main effect of sex only approached significance (F = 3.13, $P < 0.10$); the females responded somewhat more slowly (mean = 326 ms) than the males (296 ms). There were no significant interaction effects. There is other indirect behavioural (e.g., Flanery and Balling, 1979; Brown and Grober, 1983; Berlin and Languis, 1980) and morphological (Wree *et al.*, 1980) evidence that the nervous system undergoes developmental and degenerative changes which are different for the two sexes. It is of interest to note that the latter study reported sex differences in the lateralization of neuronal loss in the locus coeruleus, the point of origin for a noradrenergic system. The noradrenergic neurons ascending from the locus coeruleus to the neocortex influence the processing of sensory information. This system appears to alter the reactivity of certain visual cortex neurons, enabling them to respond to a previously ineffective stimulus (e.g., Kasamatsu *et al.*, 1981).

A recent study of lateral conjugate eye movements (de Bonis and Freixa i Baqué, 1983) reported that females tended to look more often to the right, while males tended to look more often to the left. If this finding is viewed as a sex difference in orientation bias, it is in agreement with the interactions between the sex and visual field effects on overall manual reaction time found in the present study.

Overall the female neurological subjects responded more slowly than male neurological subjects, as was the case for normal subjects. Subjects with right hemisphere lesion responded significantly more slowly than normal subjects and patients with left frontal lesions. This finding corroborates a previous report of elevated reaction times to auditory stimuli following right hemisphere lesions (Howes and Boller, 1975).

The right frontal effect of overall slowness was due to the performance of the female subjects in that group, while the right parietal effect was attributed to the male subjects (fig. 2, left side). These same two groups (right frontal females, right parietal males) showed a visual field difference in this effect. The performance of right frontal females could not be distinguished from the performance of normal males in terms of the visual field effect. Both groups responded more slowly and showed a greater effect of cue validity to the right than the left visual field targets. In contrast, the performance of the right parietal males resembled that of the normal females in that they responded more slowly and showed a greater effect of cue validity to the left than the right visual field targets. Thus what appears to be a normal sex difference in orientation bias may be reversed by a right hemisphere lesion.

The right hemisphere lesions that did not affect overall reaction time (right frontal males, right parietal females) were associated with failure to use the spatial cues (fig. 2, right side). Why were the right frontal males and right parietal females unable to use the spatial cues effectively? According to the model of voluntary attention presented by Butter (1987), the perceptual salience of a stimulus may be increased when an instruction (external or self-generated) results in the activation of a central representation of that stimulus. The activated representation then activates the mechanisms that facilitate arousal and control orienting responses. An inability to use the spatial cues (external instruction) in the present study could result from damage to any region that is directly or indirectly responsible for activation of the central representation of the target stimulus and/or for production of orienting responses, or from disconnection of any region involved in activation of the representation from the regions where representations are stored. The question as to why some subjects were unable to use the spatial cues effectively will be addressed later with the discussion of Experiment 2.

Posner *et al.* (1984) have reported that right parietal damage results in significantly slower manual reaction times to contralateral stimuli following invalid spatial cues. They attributed this finding to a deficit in the ability to disengage from a (peripheral) spatial cue presented in the contralateral visual field. This finding was not robust in the present study. A direct comparison of these studies is difficult because of differences in subject relevant variables such as age and lesion site. As noted earlier, there are data from a variety of disciplines which indicate that the measured behaviours vary with development (Berlin and Languis, 1980). The average age of Posner's neurological subjects was 69 yrs (range 61 – 83 yrs), as opposed to an average age of 37 yrs (range 17 – 57 yrs) for the present study. Of the 6 right parietal subjects in the Posner study, 1 was a woman, 2 of the males had damage extending into the frontal lobe and 1 male had no verification of cerebral damage location. If parietal and frontal lobe mechanisms work in balance, as suggested by the present and other experiments (Posner *et al.*, 1984; Rafal, 1987), lesions affecting both regions would obscure the functional dissociation of these mechanisms.

However, if methodological and subject differences are ignored and a comparison is made, the following results emerge. It was found that Posner's data, collected with a cue-target interval of 150 ms (as used in the present study) were consistent with the present data. The 1 female with right parietal damage in the Posner study had an overall manual reaction time of 555 ms and an overall effect of cue validity of 31 ms. Thus this subject is indistinguishable from the right parietal females in the present study (*see* figs 4, 5). The 5 male right parietal subjects in Posner's study showed a mean overall manual reaction time of 663 ms and an overall effect of cue validity of 248 ms (range 70–579 ms). Therefore, similar to the right parietal males of our study, Posner's subjects were slower to respond and showed a greater effect of cue validity than the female subject.

Our subjects that did not show a significant effect of cue validity (right parietal females and right frontal males), did not show evidence of the disengagement deficit shown by the Posner *et al.* patients. There were no significant differences in reaction times, regardless of the trial type condition or visual field of target. In contrast, the subjects that did show a significant effect of cue validity (right parietal males and right frontal females) exhibited possible signs of engagement/disengagement alterations. However, these were not significant findings. The right parietal males showed some indication of a contralateral disengagement deficit (reaction time for invalid condition greater for contralateral (687 ms) than ipsilateral targets (646 ms)), whereas the right frontal females showed an indication of increased contralateral engagement (reaction time for invalid condition greater for ipsilateral (730 ms) than contralateral targets (702 ms)). These trends suggest a relationship between tonic arousal/activation as demonstrated elsewhere (Ladavas, 1987) and the engagement/disengagement deficits. They are consistent with the parietal (Posner *et al.*, 1984) and frontal lobe (Rafal, 1987) findings reported previously and with the speculation that a normal sex difference in orientation bias is reversed by a lesion in the cortical region normally dominant for maintaining sensory arousal and/or motor activation to external events (fig. 2, left side).

Other recent studies that employed peripheral cues (Baynes *et al.*, 1986; Morrow and Ratcliff, 1987) have corroborated the Posner finding of a disengagement deficit following right hemisphere lesions. Similar to Posner's subjects, some degree of neglect or extinction was present at the time of testing. In fact, Morrow and Ratcliff demonstrated that the severity of neglect in their subjects was correlated with the severity of disengagement deficit. The subjects in both studies were older than the subjects in the present study and most had sustained damage that extended into the frontal lobe. As noted earlier, the present subjects did not show signs of neglect or pathological extinction at the time of testing. In addition, they were tested when their disease process was relatively stable. It is therefore possible that the present results do not reflect the disengagement deficit robustly because they represent a state of dysfunction that is less severe, more resolved or focal in nature.

It is possible that the cue-target interval of 150 ms used in the present study provided insufficient time for the subjects to disengage from the central cue prior to the onset of the target, thereby accounting for the lack of cue validity effect. A longer cue-target interval may have resulted in the disengagement phenomenon shown previously (e.g., Baynes *et al.*, 1986). This hypothesis cannot be eliminated by the present data. However, Posner's data (1984) indicated that the right parietal subjects were not captured visually by the central cue in the condition that used the same cue-target interval. Median reaction times to the contralateral target were identical following an invalid cue, regardless of central or peripheral location (740 ms). If the reduced effect of cue validity for contralateral targets found in Posner's data for the central cue (central cue effect ~50 ms; peripheral cue effect 150 ms) was secondary to slowed disengagement from fixation, then reaction time would be expected to be slower following the central than the peripheral cue regardless of its validity. This was not the case. Instead, the data suggested that the increased cue validity effect to contralateral targets was due to a facilitation of sensory processing following the valid peripheral cue (reaction time 590 ms). Median reaction time to the contralateral targets following the valid central cue was approximately 690 ms (extrapolated from fig. 4, Posner *et al.*, 1984).

Different cue-target intervals were not included in this study and therefore information regarding frontal and parietal lobe contributions to mechanisms of attentional engagement and disengagement is minimal. However, the present data suggest some ways in which these regions interact and provide clues regarding factors that may underlie individual differences in both tonic and phasic mechanisms within the right frontal and parietal lobes (e.g., sex, steroidal hormones and related neurotransmitters).

Experiment 2—saccade response

The dextral normal subjects of the present study showed no visual field difference in overall saccade reaction time. This result is in agreement with the normal subject data in Hallett and Adams (1980) and Guitton *et al.* (1985), but in conflict with the finding that dextral normal subjects respond faster to right than left visual field targets (Pirozzolo and Rayner, 1980).

This discrepancy could be due to differences in retinal eccentricity of target stimuli. The three studies that found no visual field difference in saccade reaction time used stimuli presented 10–15.3° of visual angle to the left or right of fixation. The visual field difference was found overall for stimuli presented at 2–10° eccentricity. Pirozzolo and Rayner (1980) reported a bimodal pattern in the relationship between reaction time and target eccentricity; reaction time decreased with eccentricity out to 10°, but increased at 15°. They argued that different neural mechanisms underlie the programming of saccades in the parafoveal and near peripheral visual field (geniculostriate pathway) vs the far peripheral visual field (superior collicular pathway). In this context, geniculostriate mechanisms which underlie saccade generation may be more lateralized.

Right parietal lesions elevated saccade reaction times to left (contralateral) visual field targets ($\bar{X}$ = 243 ms) relative to right (ipsilateral) visual field targets ($\bar{X}$ = 216 ms). Although this result was not significant at the 95% confidence level, it was close to significance (t test for related measures = 1.76 (df = 6), P = 0.06, 1-tailed test = 1.9). These same subjects showed significantly elevated manual reaction times to contralateral visual targets in Experiment 1. Also, a previous study reported increased saccade reaction times to contralateral stimuli following damage to the right parietal lobe (Sundqvist, 1979). These results may reflect a decrease in visual arousal and/or motor activation to contralateral targets. In the present study, the subjects with right frontal lobe lesions tended to respond faster to targets appearing in their contralateral visual field. Perhaps this finding reflects an increase in visual arousal and/or motor activation to contralateral stimuli. This trend was not found as a group effect in a previous study of saccade reaction times following frontal lobe lesions (Guitton *et al.*, 1985), although particular patients in that study occasionally showed 'express saccades' (Fischer and Ramsperger, 1984) to the contralateral side (personal unpublished observations).

The significant Subject Group × Visual Field interaction found in the manual response data of Experiment 1 and the similar trend in the saccade response date of Experiment 2 agree with a hypothesis first proposed by Denny-Brown (1956, 1958). Denny-Brown and Chambers (1958) showed in monkeys that unilateral forced manual grasping, a behaviour normally dependent upon the parietal lobe, was released by frontal lobe lesions. Conversely, parietal lobe lesions induced an abnormal reversal of this behaviour: the monkeys seemed repelled by the same stimuli that had induced the forced grasping behaviour. Based on these data they proposed that responses to environmental events are normally influenced by two opposing forces. Damage to the mechanisms of one releases the abnormal influence of the other. They hypothesized that the parietal lobe is normally responsible for the organization of exploratory behaviour in contralateral space, while the frontal lobe normally modulates the parietal lobe by inhibiting its activity.

The most striking effect of cue validity in Experiment 2 was on saccade amplitude. Compared with the normal subjects, the right frontal subjects made hypermetric saccades to visual targets in their contralateral visual field following the invalid cues and hypometric saccades to contralateral targets following the valid cues. The opposite orientation was found for the right parietal subjects. The data also indicated that the right frontal effect was due primarily to the performance of the male subjects while the right parietal effect was due primarily to the performance of the female subjects (fig. 2, right side). These results may reflect an intrahemispheric dissociation of function across sex. This interpretation is supported by the manual reaction time data of Experiment 1. A right hemisphere double dissociation of function across sex was found for overall manual reaction time and overall effect of cue validity on manual reaction time (fig. 2, left side).

The right frontal males and right parietal females were the only subjects who were unable to make effective use of the cues in Experiment 1. These same subjects showed a normal effect of cue validity on saccade reaction time. That is, they prepared to make saccades to the visual field indicated by the arrow cues in the same manner as the other subjects. These findings suggest that the dysmetria shown by the right frontal males and right parietal females was not due to a deficit in perceptual processing of the cues, but due to a disruption in the cognitive interpretation or use of the symbolic cue. Since the effect of cue validity differed depending on the location of cerebral damage, it may be that frontal and parietal lobe mechanisms normally interpret the symbolic, spatial cues in different ways.

The present data only allow for speculation on how the proposed frontal and parietal lobe mechanisms may differ. For the right frontal group, the effect of cue validity on saccade amplitude could be described as an 'under' reaction to the symbolic cue, whereas for the right parietal group the effect of cue validity on saccade amplitude could be described as an 'over' reaction to the symbolic cue. Perhaps the credulity of the cues differed for these groups. These regions may normally work together to provide a balance between two sets of instructions (e.g., believe the symbolic cue or do not), because elimination of one mechanism appears to result in the exaggerated effect of the other mechanism. Perhaps frontal lobe mechanisms normally control the selection of visual targets based on external events (in this case the symbolic cue), whereas parietal lobe mechanisms may normally control the selection of visual targets based on a different set of criteria, namely internal events (e.g., the relevance of an event based on its biological or emotional significance). The sex difference in effect of lesion implies that on average males and females use different strategies in selecting visual targets, and may provide clues regarding individual differences in these mechanisms.

There are other studies which support the proposed right frontal and right parietal lobe dissociation of function. The explanation of the saccade amplitude results is compatible with the results of other studies. For example, it has been demonstrated that frontal cortex is essential for the performance of tasks that require changes in response based on changes in stimulus context or verbal instruction set (Luria, 1966; Milner, 1964, 1982; Brody and Pribram, 1978; Petrides, 1982). These deficits are often referred to as 'inflexible behaviours' due to impaired response inhibition, but they could also be explained by an inability to use symbolic external events to control the choice of behaviourally important visual stimuli. That is, these patients may be unable to attend to the external cues that indicate how their behaviour should be changed. The social withdrawal or antisocial behaviours associated with frontal lobe damage could also be explained in terms of a deficit in monitoring external events for the maintenance of socially appropriate behaviour (Deutsch *et al.*, 1979; Kolb and Taylor, 1981). Some cognitive deficits that are associated with parietal lobe dysfunction suggest a strong link between parietal lobe mechanisms and internalized events. For example, parietal damage has been associated with the inability to retrieve or manipulate an internal visual code (Butters and Barton, 1970; Bisiach and Luzzatti, 1978; Bisiach *et al.*, 1979, 1981). Affective changes following parietal lobe damage may reflect an inability to access internal mechanisms of emotion. Anosognosia, a denial of symptoms such as homonymous hemianopia or hemiparesis, could represent a disturbance of self-evaluation and a failure to respond to an illness with the appropriate emotional concern (Critchley, 1953; Heilman *et al.*, 1978).

In summary, the findings of both Experiments 1 and 2 suggest a dissociation between frontal and parietal lobe function within the right hemisphere that varies between the sexes. If one assumes that lack of an effect of cue validity reflects an inability to attend selectively to visual stimuli in space, the parietal lobe may be a region necessary for this function in the typical female brain, while the right frontal lobe may be a critical region for this function in the typical male brain. In addition, the female right frontal lobe and the male right parietal lobe may normally be involved in maintaining visual arousal and/or motor activation, since damage to these areas resulted in a significant overall increase in manual reaction times. The significant increases in overall reaction time were seen in both visual fields and the loss of cue validity effect on manual reaction time was also bilateral. These results agree with studies suggesting that mechanisms controlling selective attention and/or arousal are lateralized to the right hemisphere (*see* Heilman and Van Den Abell, 1980).

It is hypothesized that the sex differences found in this study are due to right hemisphere differences in function for the age group studied. However, since a small number of patients composed each of the sex by lesion groups, these sex differences should be viewed with caution. Some alternative explanations for the sex differences found in this study (e.g., familial sinistrality, differences in reasoning ability) could not be adequately assessed. Also, since the subjects were all tested by the same person (S.N.-L., a female), the results would have to be replicated with a male tester to assess the possibility of an effect of the sex of the tester. However, in spite of these limitations, the consistency and magnitude of these findings strongly suggest that the anterior/posterior location of damage within the right hemisphere may differentially affect visual attention and spatial orientation, and that this effect may differ between the sexes. This sex difference could be due to genetically-determined structural differences or to structural changes in response to different environmental conditions without a concomitant genetic difference. A better understanding of the mechanisms underlying normal and abnormal visual attention and orientation to visual stimuli will be gained if lesion site and sex are considered together.

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BOOK REVIEWS

Introductory Neurology. Second edition. By James G. McLeod and James W. Lance. 1989. Pp. 33. Oxford: Blackwell. Price £11.95 (paperback).

Authors of second editions of undergraduate textbooks of clinical neurology which have justly earned laudatory reviews tend to avoid major reconstructions. Understandably they usually prefer to enjoy their success and limit their efforts to tightening a few neurological nuts and bolts. This book is a splendid exception. The text has been completely revised and several new chapters have been added. Fortunately, the style remains unaltered: crisp, clear and concise and reflecting great experience of undergraduate teaching. Consider, for example, the section on history-taking and the difficulties that many students find initially in guiding the patient's narrative: it should be 'sharpened a little here and there by an occasional direct question from the clinician, to keep the history within the bounds of relevance and to prevent it from degenerating into a list of doctors consulted, investigations ordered and opinions proffered by neighbours and casual acquaintances'. Introductory clinical courses still tend to recommend that patients should be encouraged to give an uninterrupted meandering account flavoured with free associations, opinions and Proustian introspection. I suspect that most students will find this firm guidance refreshing.

It is always intriguing to see how successfully senior clinicians with special research interests can sympathetically remain in contact with student requirements. Again the authors have succeeded admirably. They have prudently kept the topics for which they are acknowledged international authorities in modest proportions and they are generous in their acknowledgements and references. Particular mention must be made to the increased number of excellent line drawings which convey the essentials vividly and with economy. In recommending a book for junior clinical students there are a number of fine competitors but this edition of *Introductory Neurology* is still strongly recommended.

GERALD STERN

Neurology of Pregnancy. Second edition. By James O. Donaldson. *Modern Problems in Neurology*, Volume 19. 1989. Pp. 347. London: W. B. Saunders. Price £35.00.

It has always been my contention that the verbal or written presentation of scientific material can be concise without being dull, that clarity of the language (without recurring abbreviations) ensures readability, that the occasional light-hearted aside enhances rather than detracts from the scientific content, and that the paper, or certainly a book, should reflect the personality of its author. Unhappily in these days when papers are apparently written by committees, this is rarely the case. This book, the second edition of one of the volumes in the very successful Modern Problems in Neurology series, fulfills all these criteria. There has been considerable up-dating since its first appearance 11 years ago, particularly in the sections on cerebrovascular disease, epilepsy, and the use of modern diagnostic facilities. Any disorder in pregnancy, be it neurological or what-have-you, involves the management of at least two people at the same time. Whatever the disease may be that is being described, the effects on the mother have to be linked with the effects on the fetus, and the possible effects of fetal disease on the mother. The author clearly feels that his remit starts with the desire to become pregnant, or to avoid becoming pregnant, the act of conception, the period of gestation, the climax of delivery and, of course, the puerperium. The way in which he links all these stages together is most impressive. For instance, while for many women pregnancy is a cherished ambition, for others it is to be avoided at all costs. So the side-effects of the Pill appear under several headings, as do the possible neurological complications of abortion, therapeutic or criminal. His greater interests are reflected in more detailed chapters, such as those on cerebrovascular disease of all varieties, toxaemia and eclampsia, epilepsy, and muscle and movement disorders. Instructive cameos of medical history start most chapters with fascinating case descriptions from early years. He is patently less happy in dealing with headache in its various forms. Multiple sclerosis is given surprisingly short shrift, and though magnetic resonance imaging is included in this chapter (though apparently not approved in pregnancy in the States) its quite dramatic value in the diagnosis of MS is not mentioned. Maybe the media are different in our two nations, but the 'bibles' of medicine in this country—i.e., the women's magazines—send pregnant epileptics on therapy into a frenzy about spina bifida, whereas this is mentioned rather en passant, orofacial clefts being taken as the main related problem. It is so good to see that he feels the dangers of maternal and fetal anoxia from a severe epileptic seizure on stopping treatment far exceed the teratogenic possibilities of therapy. He does, however, bravely tackle the mountainous and, as he says, contradictory, literature on teratogenicity of anticonvulsants, regarding mechanism, the effects of individual drugs, and how to talk to patients about it. Counselling forms a major part of each chapter. This is a lesson we all should learn.

Reviewing books always brings me—maybe not to my colleagues—a realization of one's own ignorance. I did not know that giving magnesium sulphate to a toxaemic myasthenic could precipitate a myasthenic crisis, or indeed that a gin and tonic might do so. Clearly there has been a longstanding battle between Dr. Donaldson and obstetricians over the pathology and management of eclampsia. This section of the book is most instructive, showing the value of the administration of magnesium sulphate to be more a matter of religious faith than a scientific fact.

I wonder how many of us know about orgasmoplexy, where the woman goes into a deep sleep at le moment critique? Not, the author emphasizes, to be looked upon as a reflection on her partner's prowess, but a variant of narcolepsy. I did not know that Hippocrates considered puerperal psychosis to be due to cerebral engorgement from misdirected milk.

The conciseness referred to earlier at times causes one to raise one's eyebrows at what might seem to be dogma. 'If a women with stable myasthenia gravis wishes to have a baby, she should be advised to have a thymectomy first.' 'Fat embolism is a self-resolving illness.' He is perhaps a little off-hand with men suffering severe exertional coital headache, by saying they would be well advised to get into better shape!

Bibliographies in American publications are always extensive—one wonders who does them—but the enormous bibliography in this book is a little unusual in that after each chapter there is a large list of 'references' presumably being those specifically listed in the text, and then sometimes an even longer list of 'bibliography' being presumably sources of information not necessarily individually mentioned. If the author thinks it is unmanageable, he says so. 'The literature is in such a quagmire, no attempt is made to review it.' This was relating to vascular disease and the Pill. How well one knows the feeling. It is to his credit that nowhere does he confuse the reader by hosts of contradictory reports, just for the sake of completeness.

There are a surprising number of proofing errors, some of which require a little guesswork to sort out, but when one considers that the chapter on epilepsy alone carries about 325 references, a spelling error here and there takes little away from a book which is of obvious value to the obstetrician faced with an unfamiliar neurological syndrome, and to the neurologist, already knowing his subject, but needing the wealth of information obtainable here when faced with a patient who is, or wants to become, pregnant, and needs to know the potential problems that may arise. Strongly recommended.

EDWIN BICKERSTAFF

Neurological and Neurosurgical Intensive Care. Second edition. Edited by Allan H. Ropper and Sean F. Kennedy. 1988. Pp. 364. Rockville, MD: Aspen. Price $63.00.

The first edition of this book was published in 1983. The speed of development of intensive care management dictates frequent appraisals of the balance between what is possible and what is sensible. In no small measure the authors of this book (largely from the staff of the Massachusetts General Hospital and Harvard Medical School) succeed in this aim. Fourteen-bedded neurological intensive care units are somewhat rare in the UK and the brief summary of the range of clinical material which the editors see (as codirectors of the unit) is some guide to their undoubted wide experience. I assume that in the editors' unit patients never present ventilated or intubated prior to a diagnosis being made! Some discussion of diagnostic difficulties in patients with acute respiratory insufficiency or coma would have been welcome.

The first part of the book concerns the basic principles of raised intracranial pressure, its measurement and treatment, followed by airway management and respiratory failure: further reviews on cardiopulmonary aspects of neurological catastrophes (sic), nosocomial infection, metabolic disturbance and electrophysiological monitoring are included. The basic physiology is well explained at a high level probably beyond what many neurologists will find easy to apply in their role as 'visiting consultant' to the general medical ITU. The section on airway protection and the corollary of the assessment of bulbar function could have been expanded somewhat since, in the conscious patient at least, it is the interaction between this and respiratory function which is so important in management.

The second part of the book deals with specific disease entities. Many issues of relevance to neurologists and neurosurgeons are summarized with good up-to-date referencing. There are notable (and concise) chapters on stroke, coma after cardiac arrest, Guillain-Barré syndrome and status epilepticus, to itemize but a few. The book concludes with three chapters dealing with the diagnosis of brain death, legal aspects of decision making and ethical aspects of withdrawing treatment. The latter chapters contain much thought-provoking material (including brief summaries and commentaries of some recent US court judgements). It is easy to dismiss these issues as remote from clinical practice but those who have close contact with intensive care units will recognize much relevance.

In conclusion, this is an excellent and evenly written text. Practical guidance on ITU issues is given in addition to short reviews of recent evidence for using (or not) particular techniques and therapies. I think that many neurologists and neurosurgeons would find helpfully critical comment on aspects of their daily practice here.

C. M. Wiles

Neurosurgical Treatment of Persistent Pain. Physiological and Pathological Mechanisms of Human Pain. By J. M. Gybels and W. H. Sweet. 1989. Pp. 442. Basel: Karger. Price £88.20.

Recent years have seen progress in our understanding and management of chronic pain. The pathophysiological mechanisms whereby complex patterns of symptoms may arise and persist despite 'curative' procedure are no longer incomprehensible. Similarly neurosurgeons are no longer restricted to the time-honoured severing of peripheral nerves or the spinothalamic pathways. It is appropriate, therefore, that this volume should appear authored by Drs Gybels and Sweet who, individually, have a wealth of experience in pain surgery and have been both innovators and welcome critics within this field.

In a brief introduction they outline the current concepts of chronic pain, describe the problems faced in collating results, and comment frankly on the differences that have arisen between therapists from different disciplines. The text of the book covers, in three sections, ablative procedures, electrical stimulation and intrathecal drug administration. Topics are discussed in varying detail but in each chapter the authors present a historical review, physiological and anatomical data of relevance and some technical information on the procedures discussed. In unbiased detail they describe the results and complications of each before appending their own editorial conclusions. The 'surgical' chapters are presented logically and anatomically, progressing from procedures on cranial nerves and nerve roots through the cord and brainstem to the diencephalon and cerebral hemispheres. There is a brief chapter on pituitary ablation and, in slightly more detail, on sympathectomy. They might usefully have included a brief chapter on the nonsurgical technique of intrathecal neurolysis which can be as effective and more easily performed than percutaneous radiofrequency procedures. Despite this, a wealth of information is presented under numerous subheadings and the clinician seeking information on any ablative procedure will find it here.

Those chapters discussing electrical stimulation and the intrathecal administration of opioids are, by comparison, brief but present succinct accounts of their presumed mode of action. Although the current consensus, including that of the two authors, is to seek a physiological 'cure' for pain symptoms which one might expect from these techniques, this is not the message which they convey but rather one of typical neurosurgical conservatism.

This book is a timely successor to *Pain and the Neurosurgeon* coauthored by Dr Sweet and last published 20 years ago, and will replace it as the bible of neurosurgical pain relief. Although not encyclopaedic nor intended as a manual of technical procedures, it comprehensively covers all neurosurgical aspects of pain relief and will prove an excellent source of reference both for those actively involved and for those seeking to advise or refer their patients. It should find its way into the libraries of neurosurgical departments and any hospital supplying a pain relief service.

COLIN SHIEFF

HTLV-1 and the Nervous System. Edited by Gustavo Roman, Jean-Claude Vernant and Mitsuhiro Osame. *Neurology and Neurobiology*, Volume 51. 1989. Pp. 664. Price $120.00.

Retroviruses have long interested veterinary clinicians especially those concerned with neoplasia and diseases of the nervous system. Most medical clinicians first became aware of retroviruses with the discovery nearly a decade ago of the association between human T cell lymphotropic virus type 1 (HTLV-1) and adult T cell leukaemia (ATL). However, at first neurologists paid little attention to this virus or to the next three shown to be pathogenic in man (HTLV-2, HIV-1 and 2). The epidemic of acquired immune deficiency syndrome (AIDS) was initially seen as an immune disorder with neurological involvement being confined to opportunistic infections of the CNS, but it slowly dawned on medical clinicians that HIV-1 was like so many of the animal retroviruses in being neurotropic and caused a variety of neurological deficits including dementia, myelopathy and peripheral neuropathy. Against this background, it will come as no surprise that HTLV-1 not only causes leukaemia but is also neurotropic. Gessian and colleagues discovered in 1985 that there was a strong association between tropical spastic paraparesis (TSP) and the presence of HTLV-1 antibodies in the blood. Subsequent work not only confirmed these original observations but also showed that HTLV-1 is almost certainly the cause of TSP in the Caribbean, South America, Africa and Europe and the agent responsible for the progressive myelopathy in Japan termed HTLV-1 associated myelopathy (HAM).

HTLV-1 and the Nervous System is an account of the proceedings of a symposium held, appropriately enough, in Martinique in the spring of 1988. It also contains invited papers from others not attending the conference. The editors hope that this production is a 'comprehensive . . . state of the art reference source on the neurotropism of HTLV-1'. The book is wide ranging, containing sections on basic biology of HTLV-1 and its associated leukaemia and lymphoma, many chapters on TSP including neuroepidemiological and clinical aspects, neuropathology, immunology and pathogenesis, other systemic effects of the virus, public health problems and animal models—running in all to 664 pages. The problem with such a book is that it requires good editing since it covers vast areas of neurobiology—and the editing is not good. Its deficiencies fall into two categories, viz., inadequate explanation of specialist subjects and repetition.

The first deficiency is exemplified by the article on the molecular biology of HTLV-1 by Yoshida which contains a wealth of information that is probably unintelligible to most neurologists yet is mundane to the DNA buff. It is fascinating that 'a 4.2 kb env mRNA is spliced into a 2.1 kb pX mRNA, which then codes for $p40^{tax}$ etc., but where was the messenger editor to translate the code! The second deficiency is illustrated by the clinical chapters. If a succession of clinical scientists report their experience of a disorder like TSP from Martinique, French West Indies, France, Jamaica, Colombia, Panama, Dominica, Peru, Chile, USA, New York, sub-Saharan Africa and Okinawa, it really does require the editors to do their work properly to avoid repetition, particularly in the preamble to each article. The reader will certainly be aware of just about every feature of the disease at the end of more than 100 pages of repetition which ends with yet another article in which a subject is 'revisited'.

Some of the chapters are fascinating, for example, those on epidemiology, and there are nuggets of new information such as the data on cortical and spinal cord stimulation. Unfortunately, these prizes are so buried in the book it is doubtful they will ever be found by the enquiring reader. It is a pity that the editors flunked their task so badly because there is ample material there with which to produce a good book, a quarter of this length, that would be intelligible to clinicians and scientists alike and would be widely read.

I am afraid this book cannot be recommended.

PETER RUDGE

Mild Head Injury. Edited by H. S. Levin, H. M. Eisenberg and A. L. Benton. 1989. Pp. 288. Oxford University Press. Price £32.00.

Over the past 20 years, clinical research on head injury has been focused mainly upon severe head injury where the patient is comatose. Although the Glasgow Coma Scale defines all degrees of impairment of consciousness, it was also targeted towards precise definition of states of coma and near-coma following head injury. During this time interest in minor or mild head injury was mostly confined to the postconcussional syndrome and the phenomenon of impairment of function following minor head injury, where opinions were divided between organic brain dysfunction and malingering as the cause.

In recent years a number of developments have increased the attention paid to mild head injury. Experimental models of head injury permit injuries of all degrees of severity to be studied. Detailed neuropathological examination has revealed subtle structural changes in cases of mild head injury. New modalities for imaging the brain and measuring its blood flow and metabolism have revealed abnormalities in cases of minor head injury. Detailed examination by neuropsychologists has revealed reproducible and quantifiable deficits, particularly when tests have been specially modified or developed for use in patients with minor head injury.

The time is ripe, therefore, for an up-to-date review of an area that has now become a popular research field in the clinical neurosciences. All this can be found in this multiauthor book on head injury. Although the volume is based on a conference that was held at the University of Texas Medical Branch at Galveston, the arrangement of sections and the manuscripts written by an international field of workers outstanding in the area of head injury betray little of its origins. It is a most readable text that provides fascinating insights into many of the persisting puzzles of so-called minor or mild head injury. The areas covered include epidemiology, experimental models studied morphologically and neurochemically, imaging of the brain of patients with mild to moderate head injury, the clinical features of minor head injuries in children, and the complications that may follow minor head injury. Deficits of attention, cognition, speed of response and the neurobehavioural outcome of minor head injury are covered thoroughly. Two chapters are devoted to postconcussional symptoms and syndromes, and the last section is related to rehabilitation.

Highlights of the book include chapters by Gronwall on the effects of mild injury and data processing capacity, and by workers from the University of Virginia on head injuries sustained in sporting activities, notably boxing and American football. The puzzling condition of posttraumatic migraine is also reviewed.

This book brings together material from a wide range of sources in a compact form that is enjoyable to read and consult. The sequelae of minor head injury are common problems confronting neurologists, neurosurgeons, paediatricians, psychiatrists and many others concerned with the clinical neurosciences. This book will help all clinicians who encounter such patients, and few do not.

J. DOUGLAS MILLER

Current Problems in Epilepsy. Anatomy of Epileptogenesis. Edited by B. S. Meldrum, J. A. Ferrendelli and H. G. Wieser. 1988. Pp. 187. London: John Libbey. Price £24.95.

This book undertakes to present the current state of play in several areas of research into the neuroanatomical basis of seizures and their spread, both in man and experimental models. It is largely

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written in the form of review articles, with emphasis on the authors' original contributions. The book is readily comprehensible to the reader who is not au fait with the details of the methods employed and thus helps to build an important bridge between laboratory and clinical endeavours.

The book is essentially in 3 parts. The first 3 chapters set the scene. After a historical introduction there is a chapter on current investigatory techniques with a clear description of immunocytochemical methods for identifying the distribution of specific enzymes, amino acids and peptides. Meldrum then gives an overview of various in vivo and in vitro models of epilepsy and their correlation with human epilepsy syndromes.

The second section comprises 4 chapters detailing rodent models of seizures. These comprise sound-induced seizures in strains of mice and rats, which do not have a human parallel. Next there is a discussion of the pentylenetetrazol-induced seizures in rodents that is a model of generalized seizures. Thirdly, the model of kindled seizures and limbic status epilepticus induced via electrodes implanted in amygdala and hippocampus is discussed. Fourthly, a chapter by Patel deals with limbic seizures, induced in rodents by excitatory amino acids and cholinergic agonists. Inevitably, if each chapter is to be complete on its own, there is some overlap between these 4 chapters, but the editors have done a good job at keeping this to a minimum and the styles consistent. The experiments detailed in these 4 chapters have determined the areas of brain affected by the different seizure types and the pathways of seizure spread. More interestingly, it has been found that focal injections of inhibitory and excitatory transmission agonists and antagonists can have a profound effect on development of seizures. The critical areas differ in the different models. An injection of gamma-vinyl GABA, for example, into the thalamus suppresses seizures induced by pentylenetetrazol but not seizures produced by maximal electroshock and, in contrast, gamma-vinyl GABA injected into the substantia nigra pars reticulata inhibits electroshock but not pentylenetetrazol-induced seizures. These studies conjure up the presently rather far-fetched vision of treating intractable human epilepsies with minute doses of focally applied drugs. This approach would be considerably more sophisticated than making a lesion in a demonstrated pathway of seizure spread. The utility of these methods, however, would be severely limited by complex connections forming a network of seizure spread with much redundancy, as has been suggested in the model of electrically kindled seizures and limbic status epilepticus.

The next chapter by Nacquet *et al.* provides a detailed description of studies of photosensitivity in the cat, baboon and man and reviews data on the anatomical substrate and neural pathways that are involved in responses to photic stimulation. There is then a chapter by Wieser on depth EEG recording in patients with limbic seizures. It is interesting to compare Wieser's data with that of the animal models of limbic seizures in the earlier chapters. Spencer *et al.* address the spread of the seizures intra and intercortically and suggest that temporal lobe seizures are relatively easily lateralized because spread to the contralateral hemisphere is by the hippocampal commissure and subcortical structures and not via the corpus callosum. In contrast, in frontal lobe seizures interhemispheric spread is so rapid, via the corpus callosum, that even depth electrodes may fail to lateralize seizure onset. Further study of patterns of seizure spread is clearly necessary and may lead to useful treatments with interruption of neural pathways.

The chapter on positron emission tomography (PET) by Henry *et al.* forms a useful introduction to the jargon, scope and more importantly, the limitations and pitfalls of PET methodology, and reviews the findings to date with blood flow, glucose and oxygen utilization studies and the beginnings of the more interesting era of studies with specific ligands. Lastly, there is a brief review of the classification of human epilepsies. This last chapter is more meaningful if read in conjunction with the recently published proposals of the International League Against Epilepsy Commission on classification.

In conclusion, this very reasonably priced book is recommended to clinicians who want to update themselves on what basic scientists are doing to elucidate the mechanisms and pathways of seizure spread, and vice versa. We should look forward to a second edition of this book in a few years time that details progress in the intervening period.

J. S. Duncan

The Neuropathology of Temporal Lobe Epilepsy. By C. J. Bruton. Maudsley Monographs No. 31. 1988. Pp. 158. Oxford University Press. Price £20.00.

The Maudsley Hospital study of temporal lobe epilepsy and its surgical treatment must surely now be recognized as one of the most outstandingly productive multidisciplinary research programmes in the field of psychiatry that there has ever been. In this volume Dr Bruton has, with great temerity, assumed the heavy task of documenting, tabulating and correlating the clinical neurosurgical and neuropathological data, originally as part of his MD thesis, but now presented in monograph form for general readership. In this he has attempted, as he says in the Introduction, to 'crystallise the more pertinent findings especially those relating to the long term effects of surgery according to the different types of abnormality in the temporal lobes'. This documentation, tabulated both in the text and in the detailed appendices, will undoubtedly be of considerable service to later students and very usefully summarizes the most important conclusions from the study. It must be said at the outset, however, that there are several aspects of the monograph that I confess to find unsatisfactory. Not only are there several points about his approach to the underlying neuropathology with which I find it difficult to agree, but the way Dr Bruton has underplayed his account of this important study cannot be regarded as anything but a missed opportunity to place this remarkable episode in historical perspective.

As one who was personally involved fairly early in the surgical series, being co-opted on a part-time basis from an appointment in the Pathology Department at Guy's Hospital, I find it difficult to refrain from commenting upon the historical background of this study, and make no apologies for trying briefly to make good this deficit. Murray Falconer, who was undoubtedly the main driving force that kept all the collaborators concentrated on the central problem over many years, was a remarkable and very determined man, and I do him no discredit when I say that he also had a strongly competitive spirit. In leading this project he undoubtedly set out to improve upon the earlier studies of Wilder Penfield in the surgical treatment of temporal lobe epilepsy. In this he may have been more fortunate than his colleague in Canada, even though the latter, too, had excellent back-up support at the prestigious Montreal Neurological Institute, for at the Maudsley Hospital Murray Falconer had not only an outstanding team of psychiatric, electroencephalographic and radiological colleagues, but also he was uniquely blessed in having Alfred Meyer to handle the all-important morphological side of the project. Meyer's background was exactly right for the job; for earlier in his career in Germany he not only trained as a psychiatrist, but he had worked closely with Spielmeyer who had made some of the most original contributions to the problem of the selective vulnerability of hippocampal neurons, especially in the epileptic process. For Meyer, then, this was a golden opportunity to examine the temporal lobes from still-living subjects, who were under intense clinical scrutiny both in the search for likely underlying mechanisms of the lesions responsible for the temporal lobe seizures as well as for the results of temporal lobe ablation. But Meyer's department was furthermore blessed by the presence of Elisabeth Beck who brought to the study the excellent German histological tradition with a thoroughness that was in large part responsible for the completeness of the anatomical studies that followed. I knew the value of these methods for it was from her beautiful preparations that I discovered, with amazement, for the first time the architecture of the brain in the thick, cresyl violet stained celloidin sections, having been brought up on thin paraffin sections that were standard at that temple of general pathology, the Bernhard Baron Institute. Above all these advantages, however, it was Murray's surgical skill in removing the anterior two-thirds of the temporal lobes intact, as far as was possible, with the medial structures, that was crucial to the anatomical analysis that followed. Dr Bruton rightly pays tribute to this critical factor upon which the success of the whole operation depended.

The historical process initiated in this study extended with time to involve on the one hand Corsellis, and more recently Bruton himself, at Runwell Hospital with its excellent accumulated collection of material from epileptic and other subjects, and on the other to the experimental studies of Brierley and subsequently, Meldrum, that laid the foundation for our present understanding of the mechanisms underlying the basis of the selective vulnerability of hippocampal neurons to epilepsy, anoxia and other forms of metabolic stress. More lately ideas for the control and limitation of this type of excitotoxic damage by pharmacological means are now emerging from Meldrum's experimental work. Without the initial multidisciplinary attack upon this clinical problem, none of these other studies would have found their realization in the way that they did. It was with this historical sequence that I am happy to have been involved with in a minor way and that Dr Bruton in this slender monograph summarizes, albeit rather laconically and with only a scanty discussion of the theoretical background to the problem.

Despite the numbers of reports that eventually emerged from this thorough clinical and neuropathological attack on the problem of temporal lobe epilepsy, one must not ignore the fact that Wilder Penfield did indeed demonstrate most of the pathological changes that were subsequently disclosed more completely in the later Maudsley study. While he may have misunderstood the nature of the sclerotic changes found in the medial regions of the excized temporal lobe, Penfield certainly realized their importance in the genesis of the epileptic disturbances. The descriptions of his colleague Earle, too, while necessarily incomplete because he did not have the major part of the lobe intact, clearly showed the essential morphological changes, including the hamartomatous lesions that I was later fortunate to be able to explore and describe more fully. These important matters of priority need to be noted here as they are passed over rather cursorily by Dr Bruton when discussing the neuropathology of the lesions.

In this monograph Dr Burton briefly sets out the clinical criteria upon which surgery was decided and the procedure adopted for the patient study and follow-up, preliminary to making detailed clinicopathological correlations. The histological basis for classifying the case material, a critical point for these subsequent correlations, is dealt with in some detail but does at certain points give cause for worry, though some of these criticisms, it must be confessed, are of little relevance to the main theme of the study, which was the ultimate consequences of surgical ablation of the lobe. The more general processes such as trauma, inflammation and vascular lesions cause little trouble and in a sense are of less aetiological interest. These are the understandable accidents of life with little regional specificity. The aetiological lesions of greater interest, central to the second most significant pathological change after the better appreciated hippocampal sclerosis, are those derived from what are likely to be faulty processes of development, sorting or migration of neuronal and glial cells. Unfortunately, Dr Bruton sidesteps detailed discussion of the underlying neurobiological principles involved by inventing, rather irrationally and unnecessarily in my view, a new term of 'alien tissue' which embraces both malformed and maldeveloped neuronal and glial cells as well as vascular malformations. The term does not add to the clarity of the discussion, throws no new light on their origin and nature, and moreover does not conjure up any theoretical ideas that might encourage constructive thought about these malformations. There is no doubt that several types of developmental disturbance were disclosed in this surgical series, each being expressed in the different types of change described. From what we now know of the complexity of developmental processes in cortical formation, some instances of these are inevitably more likely to occur in the temporal lobe than in any other brain region, as I have pointed out elsewhere, simply because this is the latest part of the human brain to reach full development, in which the dwindling mantle layer of His, now better known as the subependymal layer or the ventricular zone, persists for longest. The more protracted the developmental process the more likely by necessity are the chances for aberrations to occur in the mitotic and migrational steps needed. This generalization may not be true for the focal dysplasias which appear to be found in many cortical regions in addition to the temporal cortex and which are rather stereotyped in structure, but it certainly seems true for the hamartomatous glial and neuronoglial formations. These seem to be found almost exclusively in temporal lobe regions and it must be significant that despite their having been described for more than 30 years there have not been any published cases for any other brain region, so far as the reviewer is aware. Moreover, there is little evidence that has been adduced during this time for their malignant transformation, despite their regular occurrence in about 10% of the operative temporal lobe material. The descriptive term, 'hamartoma', coined by Albrecht for 'malformations in which the various tissues of the part are present in improper proportions or distribution, with prominent excess of one particular tissue', to quote Rupert Willis, is not only accurate for these formations but is to some degree hallowed by time, for what that is worth, and anyhow at least is generally understood. There seems to be no real reason for Dr Bruton to change this. I suspect, however, that he may not have completely understood my efforts to describe these formations for when he singles out on page 54 et seq. one descriptive passage for comment, he misquotes and thus seriously distorts my interpretation of the nature of this lesion. This is a pity, but of course makes no difference to the much more important matter of the clinical consequences of the operation.

In the 294 cases now accumulated Dr Bruton, in a series of tabulated clinicopathological correlations, shows that several very important aetiological factors have been confirmed, regardless of the causal nature of the hamartomatous lesions. Important correlates occur with age of onset of epilepsy, the Ammon's horn lesion being associated with the earliest onset, while the glial-neuronal hamartomatous lesions are the next earliest. Of interest in this connection is that epilepsy associated with the focal cortical dysplasias are significantly later than those with other types of pathological change, and moreover their seizure pattern was less likely to be influenced by operation. Of more general interest is the emerging relation between the psychosocial outcome of the operation and the underlying pathology; it turns out, in fact, that the more definite the pathological state the better is the outcome. Throughout the study this correlation was most striking with the Ammon's horn sclerosis group which consistently had the best outcome from surgery. More doubtful was the relationship between any improvement in aggressiveness and the underlying pathology, and in fact any improvement that took place at all may well have been due to the operation itself rather than any other factor. But what may perhaps turn out to be the most significant long-term outcome of the Maudsley study is the realization, which grew as the study was extended, that there was a distinct association between damage to the medial temporal lobe and schizophrenia-like psychosis. It is of relevance to this observation that in the recent clinical and pathological investigations carried out by Dr Crow and his colleagues at Northwick Park, which included Dr Bruton, this originally vague impression has now begun to crystallize into the realization that indeed there seems to be a faulty development of the cortical architecture in the medial temporal region in cases of schizophrenic psychosis uncomplicated by epilepsy. Is a solution to this problem, too, going to be the ultimate outcome of the Maudsley research programme begun in the 1950s? It would certainly be a considerable achievement if this turns out to be so. Perhaps one day someone will write the full story with all its ramifications of this enterprise. In the meantime the factual details are well recorded and correlated in Dr Bruton's useful monograph.

J. B. CAVANAGH

Pathology of Tumours of the Nervous System. By Dorothy S. Russell and Lucien J. Rubinstein. Fifth edition. Revised by L. J. Rubinstein. 1989. Pp. 1012. London: Edward Arnold. Price £110.00.

Since the first edition was published in 1959, 'Russell and Rubinstein' has held pride of place among books on the pathology of tumours of the nervous system. The stature of the first four editions is legendary. So, how does the fifth edition compare with the first four?

Greatly enlarged to 1,000 pages, the fifth edition is encyclopaedic in its content and is a tribute to Lucien Rubinstein's skill in gathering information from his own work, from the many tumours referred to him and from the literature. The book is set out in the familiar format of previous editions. The first two chapters cover the general aspects of tumours of the nervous system, oncogenesis and the experimental induction of tumours. In addition to the epidemiological data regarding the general incidence of tumours, there is a clear and concise account of neoplastic transformation in the nervous system. Although there is obviously not room for a detailed treatise on the molecular biology of oncogenesis, there is a useful and clear account of this subject in the first chapter. This section is particularly valuable as it points towards future unifying trends in neuro-oncology whereas the bulk of the book adheres very much to the classical concept of subdividing tumours into an increasing number of histologically defined groups. From the practical point of view, the section on the immunocytochemical aspects of cerebral tumours will be very valuable for those concerned with the diagnosis of tumours. There is a concise discussion of markers (or signposts) and their use in placing tumours into the classical neuro-oncological groupings.

The initial general section is followed by a long and detailed chapter on tumours of central neuroepithelial origin. This is a very useful and well-illustrated account of astrocytic, oligodendroglial, ependymal, choroid plexus and neuronal tumours with detailed descriptions of many of the histological variants. Unfortunately, the author is rather dismissive of the concept of primitive neuroectodermal tumours and the useful and very extensive work done by Rorke and her colleagues is not quoted. In the following chapters, meningeal, peripheral nerve sheath tumours, lymphomas, vascular tumours and tumours of maldevelopmental origin are covered. As expected, this volume is an authoritative account and the bibliographies are well up-to-date. Many of the illustrations from previous volumes are recognized in these chapters but there are also additional pictures. The only colour illustrations, however, are gathered as an isolated block at the front of the book and in this position they bear little relation to the text.

The chapter on phacomatoses covers the advances in molecular genetics that occurred in this field right up to the time of publication. Sections on metastatic tumours and the effects of tumours on the nervous system are informative and well written. The book ends with two chapters on tumours of peripheral neuroblasts and ganglion cells and on paragangliomas.

Inevitably, the book is a rather personal account of cerebral tumours and as such imparts much of the experience that the author has gained from his long association with the subject. Most, if not all, neuropathologists will welcome the appearance of the fifth edition and will delve with interest among its pages; it is a worthy successor to the first four editions. Although the amount of clinical information and discussion of neuroimaging are necessarily limited, the encyclopaedic nature of the book undoubtedly establishes its value as a reference volume for pathologists, neurosurgeons, neurologists, neuroradiologists and basic neuroscientists.

R. O. WELLER

The Computing Neuron. Edited by R. Durbin, C. Miall and G. Mitchison. 1989. Pp. 417. Wokingham: Addison-Wesley. Price £24.95.

The study of neural computation is one of the growth areas both in academe and in industry, a fact not lost on Addison-Wesley, who have introduced their Computation and Neural Systems Series to meet this expanding market. The present volume, *The Computing Neuron*, addresses both artificial and real networks of neurons, with the aim of bringing these two divergent kinds of study back together. This is an entirely sensible and important goal as the two activities ought to complement rather than to confuse each other.

The editors themselves provide the first 3 chapters, in which they attempt to introduce the key issues. I certainly applaud their deliberate distinction of real 'neurons' as studied by biologists vs the imaginary ones used by mathematicians and engineers, which the editors term 'units'. This simple device should in itself significantly reduce confusion. These introductory chapters are broad; they also are a bit sketchy. No doubt this is due to a lack of space, but I suspect that an interested novice in the field might find this treatment difficult. However, a disk of demonstration programs (for the Apple Macintosh) is available from the editors at £12 (US $20), which provides an imaginative solution to this problem. The copy I ordered arrived quickly and, apart from some problems in reading the explanatory notes off the disk, it proved an effective means of enlivening the basic ideas of artificial neural computation. I would recommend that biologists buying the book should also get the disk.

The book is based on a meeting held during the summer of 1988. I was pleasantly surprised at its quality. The individual chapters have, on the whole, been taken seriously by their authors; they have been written with reasonable care, provided with suitable original illustrations, and in many cases updated to include references from 1989. The index is short, but quite well prepared, and the production is to a good standard. All pretty impressive at the price. Topics range from the electrical properties of single pyramidal cells (Stratford *et al.*) and plasticity in monosynaptic relays (Sejnowski *et al.*) through simple networks both invertebrate (e.g., Brown, Burrows and Laurent) and vertebrate (Roberts, Atwell), to quantitative analyses of higher functions such as perception and memory (e.g., Barlow and Foldiak, Rolls, Poggio *et al.*, Wang *et al.*).

One limitation that a conference publication cannot escape is that contributions are limited to those who could be present in Cambridge (UK) during the summer of 1988. As a result there are some omissions; for example, in my own field of hippocampal physiology, the more localized and specific models of R. D. Traub would have complemented the more global account provided by Rolls. Nevertheless, my overall impression is that this book provides an interesting mix of chapters with varying slants on the issue of how neurons and neural networks transform and store information. It represents a serious stab at reversing the divergence of the studies of real vs imaginary neural networks, and as such should be applauded.

JOHN G. R. JEFFERYS

Brain Anatomy and Magnetic Resonance Imaging. Edited by A. Gouaze and G. Salamon. 1988. Pp. 189. Berlin: Springer. Price DM 156.00.

Anyone buying this strange little book could only find the title, although it accurately describes much of the contents, misleading. The 14 pieces which comprise it include an interesting, but unoriginal 24 page essay on the phylogeny of the sacrum (without reference to the brain or to imaging), and a 5 page case report (of syringomyelia). The French concept of 'pathological radioanatomy' possibly legitimizes 4 chapters concerned mainly with pathology (of intracranial blood vessels, the cerebellum, cerebellopontine angle and of vascular lesions in the posterior fossa—the latter based on 6 cases, whose captions confuse increased and decreased signal), leaving 7 chapters of interest to someone attracted by the cover, plus a perfunctory paper on the child's petrous bone.

French obsession with stereotaxy and cortical anatomy underlies two contributions genuinely dealing with anatomy and MRI, but their major conclusion seems to be that cortical anatomy is disappointingly variable! Work such as that presented at the 1989 International Congress of Radiology in Paris suggests that computer-generated MRI simulations of the surface of the brain and the overlying skull as seen during the surgical approach could rapidly render such data irrelevant. Two chapters (credited to no less than 15 authors) both cover, with marked differences in detail, the hippocampal formation and limbic system. The one by Tom Naidich and his colleagues is so densely packed with information that some of the rather small figures are difficult to take in, and the book designers, facing almost insoluble problems, have faltered, placing 20 lines of a complex legend overleaf from the images concerned. Other anatomical articles concern the visual pathways; that on the chiasmatic cistern is interesting but brief. A chapter on what the authors term the 'transverse fissure' deals with the ambient cistern, not with the transverse fissure of British anatomists, and reproduces without evident acknowledgement diagrams published in 1985 by Chakeres and Kapila (*Neuroradiology*, 1985; **27**, 383–389). This highlights one of the defects of the book: while usually comprehensible, English versions of some of the French texts are, in their own words, 'generally of little satisfaction'.

The meeting of which these are the proceedings no doubt appeared more cohesive to its participants, but I doubt that many who were not there will feel that the interest of this book justifies its substantial price.

IVAN MOSELEY

Progress in Catecholamine Research. Edited by A. Dahlström, R. H. Belmaker and M. Sander. Volume 42A. Pp. 613. **Basic Aspects of Peripheral Mechanisms.** Volume 42B. Pp. 592. **Central Aspects.** Volume 42C. Pp. 506. **Clinical Aspects.** 1988. New York: Alan Liss. Price $175.00.

According to the Preface of these volumes more than one thousand people attended the Sixth International Catecholamine Symposium held in Jerusalem in the summer of 1987; these three books are the proceedings of this meeting. The editors further inform us that certain misgivings expressed in the early stages of planning the meeting included the sentiment that 'catecholamines were old hat . . . they should be left quietly to fade away'. It is not surprising that the catecholamines show no sign of fading away, but it is perhaps curious that they show no sign of being relegated to the sidelines of the international biomedical research effort. This is especially curious for those interested in brain function, where the spectacular diversity of putative neurotransmitters already on the table combined with the clearly ubiquitous importance of certain other classes of neurotransmitter (e.g., excitatory amino acids) must surely comprise a very potent sidelining force. Why has catecholamine research played such a central role in neurochemical investigation of brain function? Two classes of explanation may be put forward: first, that this is a consequence of the historical context of early development of methods to study catecholaminergic neurons; secondly, that it reflects the true influence of these neurons on brain function, and dysfunction (their numerical insignificance belies their functional role). These of course are not mutually exclusive possibilities, and it may be reasonable to expect that these three volumes might cast some light on their relative importance in the continuing durability, vivacity and sheer size of catecholamine research. This is strikingly the case, since these pages provide eloquent testimony of the view that the historical/methodological explanation is not sufficient.

Each of these volumes comprises 1 of the 3 parts of the proceedings, each being made up of close to one hundred individual contributions. Part A, *Basic Aspects and Peripheral Mechanisms*, covers catecholamine synthesizing enzymes, transport and uptake systems, presumably under the rubric 'Basic'. This is followed by sections on a variety of 'peripheral' topics, each section ranging in size from 1 chapter (differentiation) to 11 (adrenal chromaffin cells). Interestingly, studies on normal adult peripheral neurons are not prominent. Included in Part A is a section on catecholamines in invertebrates which is perhaps most welcome to those of us who seldom venture that far from home. The second volume, Part B, *Central Aspects*, starts with its longest section, entitled simply 'Dopamine', followed by the closely related section on Parkinson's disease and MPTP. We then move on to the less predictable, and perhaps therefore more interesting, sections on primate cerebral cortex, catecholamine-peptide interrelationships, control of endocrine systems, sympathetic nervous system, blood pressure and more. The clinical studies represented in Part C cover the expected range of extrapyramidal syndromes, schizophrenia, affective disorders and related pharmacology, ending with sections on ageing and anaesthesia. This is a collection of mostly high quality contributions bringing together much material which is otherwise widely dispersed in the literature.

In such a large collection of chapters (almost 300 of about 6 pages each), organization is of paramount importance. Perhaps inevitably in a venture of this size there are instances when the organization is a little obscure. The choice of contributions chosen for the introductory section in the first volume is strange. As mentioned above, a section on Parkinson's disease as well as sections on addiction and sleep appear in Part B, rather than in the clinical Part C. Organization between volumes is particularly significant in work as expensive as these since it permits rational purchase of individual volumes. An abiding problem with large proceedings collections is that the published work is governed more by the meeting of which it is a spin-off, rather than the publication in hand. Combined with the delay in publication (you do not go to a collection such as this as an alternative to reading the current literature) this inevitably leads to the question, who needs them? Multivolume collections such as these are, of course, meant, not just to pad out the publication list of participants, but to be works of reference, and this example is well enough written and presented to serve this purpose. However, there must be many like myself who, looking for information on a selected subject, will lack the discipline to resist the temptation to dip and delve, treating these volumes more as an anthology on an old and favourite theme. There are rich pickings here indeed, giving the lie to the groan elicited when these volumes first appeared on this reviewer's desk.

M. R. Boarder

ANNOUNCEMENTS

European Neurological Society

The second meeting of the European Neurological Society will be held at the Metropole Hotel, Brighton, UK, between June 30 and July 4, 1990. On June 30 and July 1 there will be six teaching courses on: Management problems in neurology I and II; Movement disorders; What you need to know about new techniques; Neuro-ophthalmology; and Neurorehabilitation. The Scientific programme (July 2–4) includes five symposia (on Retroviruses and the Nervous system; Epilepsy; Basis for recovery in neurology; Behavioural neurology; and Molecular basis of neuromuscular disease), and platform and poster sessions. Further information from Concorde Services Ltd, 10 Wendell Road, London W12 9RT, UK, tel. 01 743 3106, Fax 01 743 1010.

International Society of Neuroendocrinology

The Second International Congress of Neuroendocrinology will be held in Bordeaux, France, on June 24–30, 1990. Information may be obtained from Bordeaux Congres, 333000 Bordeaux-Lac, France (tel. 56.50.84.49, telefax 56.43.17.76).

Fifteenth International Symposium on Cerebral Blood Flow and Metabolism

This will be held in the James L. Knight International Center, Miami, Florida, on June 1–6, 1991. Enquiries and requests for registration and abstract forms should be addressed to Ms Jenny Bernal, Conference Coordinator, BRAIN-91, University of Miami Conference Center, 400 SE Second Avenue, Miami, Florida 33131, USA.

First International Conference on Psychology and the Performing Arts

This will be held at the Institute of Psychiatry, London, on July 5–7, 1990. Further information may be obtained from Dr Glenn Wilson, Department of Psychology, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK (tel. 01 703 5411, ext. 3254/3245).

Third International Brain Workshop on Neurodevelopment, Aging and Cognition

This will be held in the Interuniversity Center, Dubrovnik, on May 7–10, 1990. Further information may be obtained from Dr S. Knezevic, Department of Neurology, University Hospital Rebro, Kispaticeva 12, 41000 Zagreb, Yugoslavia.

Fyssen Foundation 1990-1991 Fellowships

The Foundation will award a certain number of fellowships for the training and support of research scientists working in disciplines relevant to the aims of the Foundation such as ethology, palaeontology, archaeology, anthropology, psychology, epistemology, logic and the neurosciences.

The fellowships will be granted to French scientists wishing to work abroad and to foreign scientists wishing to work in French laboratories. Study grants will normally be given for one year but may be extended up to three years. Applications should be made on a form obtained from the Foundation and should include a curriculum vitae, a list of the applicant's publications, the names of two senior scientists whom the applicant has asked to send testimonials to the Secretariat of the Foundation, and a letter of acceptance from the inviting laboratory.

Completed applications (15 copies) should be sent to the Secretariat of the Foundation, 194 rue de Rivoli, 75001 Paris. Applications must be received by March 31, 1990.

Twenty-fifth Canadian Congress of Neurological Sciences

This will be held at the Banff Springs Hotel, Banff, Alberta, on June 27–30, 1990. For information, please contact the Permanent Secretariat, Canadian Congress of Neurological Sciences, 116C, 1330-15 Avenue SW, Calgary, Alberta, Canada T3C 3N6.

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The Guarantors of Brain are prepared to consider applications for part or all of the costs incurred by clinical and nonclinical neuroscientists based in the United Kingdom wishing to visit laboratories or clinical departments at home or abroad. Two schemes exist.

1. Individuals aged under 40 years may apply for the costs of short visits. Applications will be considered for attendance at scientific meetings which relate directly to the applicant's research interests. Only exceptionally will applications to attend larger international conferences be considered. Awards of up to £1000 will be made throughout the year. The Guarantors encourage applicants to meet part of their costs from other sources. Applications should be submitted at least two months before the planned date of departure.

2. Individuals of any age may apply for a limited number of awards which will enable a neuroscientist to spend several weeks visiting a clinical department or laboratory in order to learn new techniques which will subsequently be used to develop or supplement existing research. Up to £5000 will be available to cover travel, subsistence and recurrent expenses incurred in the host department. Applications will be considered during May and November of each year.

The following documents are required for awards under each scheme:

1. an abbreviated curriculum vitae with a list of publications;
2. an account of the purpose of the visit;
3. the names of two referees;
4. a letter of invitation from the host department;
5. a statement of the costs with details of related applications;
6. a list of previous awards given by the Guarantors of Brain.

Four copies should be sent to Professor Alastair Compston, Honorary Secretary and Treasurer to the Guarantors of Brain, Department of Neurology, Addenbrooke's Hospital, Cambridge, CB2 2QQ (Tel. 0223 217091).

All successful applicants are expected to submit a short report of the visit on their return.

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VOLUME 113 · PART III · JUNE 1990

Recency and frequency discrimination in the amnesic patient H.M. H. J. Sagar, J. D. E. Gabrieli, E. V. Sullivan and S. Corkin 581

Effectiveness of different task paradigms in revealing blindsight. M. Corbetta, C. A. Marzi, G. Tassinari and S. Aglioti 603

Cognitive and motor deficits in the acquisition of an object retrieval/detour task in MPTP-treated monkeys. J. R. Taylor, J. D. Elsworth, R. H. Roth, J. R. Sladek, Jr and D. E. Redmond, Jr 617

The aetiology of transient global amnesia. A case-control study of 114 cases with prospective follow-up. J. R. Hodges and C. P. Warlow 639

Quantitative assessment of class II molecules in normal and pathological nerves. Immunocytochemical studies in vivo and in tissue culture. E. Scarpini, R. P. Lisak, S. Beretta, M. Velicogna, R. Doronzo, M. Moggio, S. Jann and G. Scarlato 659

Monoclonal antibodies against sensory neuron specific antigens define the extent of neuronal abnormality in the *mf* mutant rat. F. Scaravilli, T. M. Jessell, J. Dodd and L. Chimelli 677

Abnormal vibration-induced cerebral blood flow responses in idiopathic dystonia. L. W. Tempel and J. S. Perlmutter 691

A quantitative study of sensory function in hereditary spastic paraplegia. W. Schady and A. Sheard 709

Familial cerebral amyloid angiopathy with nonneuritic amyloid plaque formation. G. T. Plant, T. Révész, R. O. Barnard, A. E. Harding and P. C. Gautier-Smith 721

Troubled letters but not numbers. Domain specific cognitive impairments following focal damage in frontal cortex. S. W. Anderson, A. R. Damasio and H. Damasio 749

Visual control of balance in cerebellar and parkinsonian syndromes. A. M. Bronstein, J. D. Hood, M. A. Gresty and C. Panagi 767

Effects of brainstem lesions on the masseter inhibitory reflex. Functional mechanisms of reflex pathways. B. W. Ongerboer de Visser, G. Cruccu, M. Manfredi and J. H. Th. M. Koelman 781

Synapses, axonal and dendritic patterns of GABA-immunoreactive neurons in human cerebral cortex. Z. F. Kisvárday, A. Gulyas, D. Beroukas, J. B. North, I. W. Chubb and P. Somogyi 793

The bulbocavernosus reflex. A single motor neuron study. D. B. Vodušek and M. Janko 813

Oculomotor disturbances during visual-vestibular interaction in Wallenberg's lateral medullary syndrome. W. Waespe and W. Wichmann 821

Book reviews 847

Announcements 855

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Continued on inside back cover

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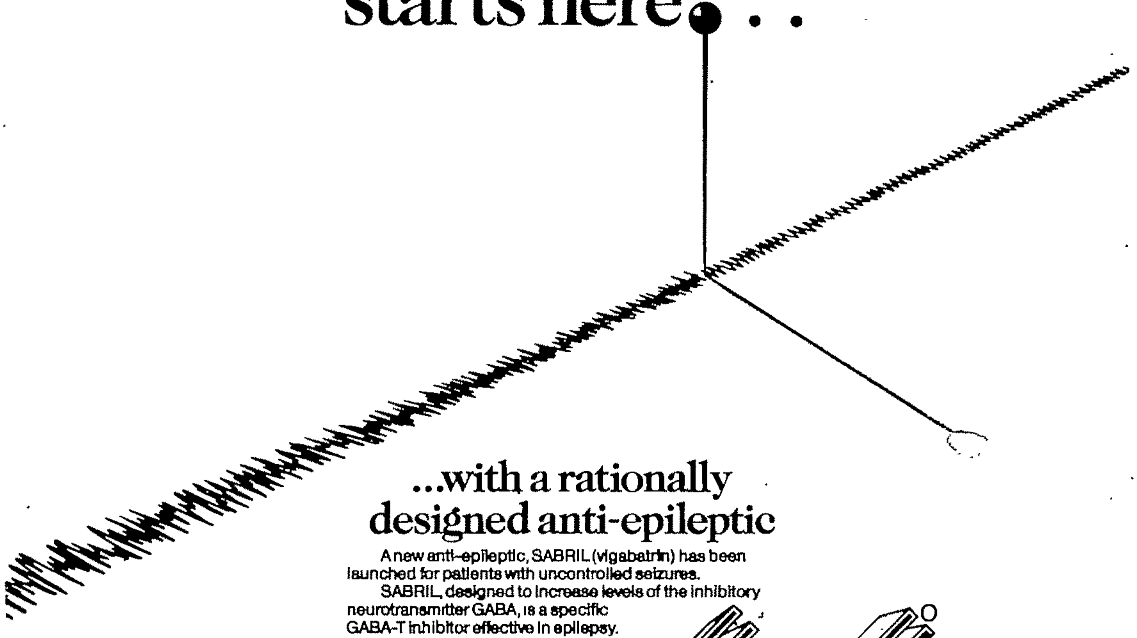

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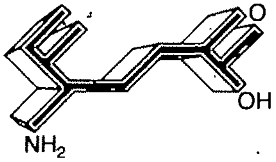

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Sabril Abridged Prescribing Information ▼

Presentation White, oval biconvex tablets with a breakline on one side and SABRIL on the other. Each tablet contains 500 mg vigabatrin. **Uses** *Mode of Action* A selective, irreversible inhibitor of GABA-transaminase. Treatment leads to an increase in brain levels of GABA (gamma aminobutyric acid) *Indications* Indicated for the treatment of epilepsy which is not satisfactorily controlled by other antiepileptic drugs **Dosage and Administration** For oral administration once or twice daily and may be taken before or after meals *Adults*. The recommended daily starting dose is 2 g (4 tablets) which should be added to the patient's current therapeutic regimen The dose may be increased or decreased in 0.5 g or 1 0 g increments depending upon clinical response and tolerability. Increasing the dose above 4g/day does not usually result in improved efficacy. There is no direct correlation between plasma concentration and efficacy. 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Reduced doses should be used and patients monitored closely for adverse events such as sedation and confusion *Warnings* · Animal safety studies indicate that vigabatrin causes intramyelinic oedema in the brain white matter tracts Currently there is no evidence to suggest that this effect occurs in man However, it is recommended that patients treated with Sabril are closely observed for adverse effects on neurological function Details of animal findings are given under "Further information" in the full product data sheet *Effects on driving ability* Drowsiness has been observed and patients should be warned of this possibility before treatment. Special care should be taken by patients driving, operating machinery or performing any hazardous task. *Side-effects*. Adverse events are mainly CNS related. The following events have been reported but in most cases the relationship to vigabatrin has not been established. drowsiness and fatigue, dizziness, nervousness, irritability, depression, headache and less commonly confusion, psychosis, memory disturbance and vision complaints such as diplopia Other adverse events reported include weight gain and minor gastrointestinal side-effects In children excitation and agitation have been seen. The sedative effect of vigabatrin decreases with continuing treatment. As with other antiepileptic drugs, some patients may experience an increase in seizure frequency with vigabatrin Patients with myoclonic seizures may be particularly liable to this effect There is no evidence of neurotoxicity in humans. Tests done to confirm lack of significant adverse effect on neurological function include evoked potentials, CAT scans, magnetic resonance imaging, CSF analyses and in a small number of cases, neuropathological examinations of brain specimens. Laboratory data indicate that Sabril treatment does not lead to renal or hepatic toxicity Decreases in SGOT and SGPT have been observed and may be a result of inhibition of these transaminases by Sabril Chronic treatment with Sabril may be associated with a slight decrease in haemoglobin which rarely attains clinical significance *Drug Interactions* · Sabril is not metabolised, or protein bound and does not induce hepatic cytochrome P450 or drug metabolising enzymes so interactions with other drugs are unlikely In clinical studies a gradual reduction of about 20% in plasma phenytoin concentration has been observed. The mechanism is not understood but this is unlikely to be of therapeutic significance. No clinically significant interactions have been seen with carbamazepine, phenobarbitone or sodium valproate in clinical trials *Overdose:* There is no specific antidote and the usual supportive measures should be employed Overdoses of 14 and 30 g of Sabril have been reported without any sequelae. **Pharmaceutical Precautions** None. **Legal Category** POM **Package Quantities** Blister strips of 10 in cartons of 100. **Product Licence Number:** PL 4425/0098. **NHS Price:** pack of 100 tabs £48 00. **Date of Preparation:** October 1989 You must refer to the full prescribing information before administering Sabril. Further information including full product data sheet is available from the Licence Holder Merrell Dow Pharmaceuticals Ltd , 1, Furzeground Way, Stockley Park, Uxbridge, Middx UB11 1BE 1 Browne TR et al Neurology 1987; 37: 184-189 2 Mumford JP Br J Clin Pract 1988, 42 (Suppl 61) 7-9. 3 Pedersen SA et al Acta Neurol Scan 1985; 72: 295–298. 4. Remy C, Beaumont D BR J Clin Pharmac (1989) 27, 125S-129S.

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VOLUME 113 · PART III · JUNE 1990

Recency and frequency discrimination in the amnesic patient H.M. H. J. Sagar, J. D. E. Gabrieli, E. V. Sullivan and S. Corkin 581

Effectiveness of different task paradigms in revealing blindsight. M. Corbetta, C. A. Marzi, G. Tassinari and S. Aglioti 603

Cognitive and motor deficits in the acquisition of an object-retrieval/detour task in MPTP-treated monkeys. J. R. Taylor, J. D. Elsworth, R. H. Roth, J. R. Sladek, Jr and D. E. Redmond, Jr 617

The aetiology of transient global amnesia. A case-control study of 114 cases with prospective follow-up. J. R. Hodges and C. P. Warlow 639

Quantitative assessment of class II molecules in normal and pathological nerves. Immunocytochemical studies in vivo and in tissue culture. E. Scarpini, R. P. Lisak, S. Beretta, M. Velicogna, R. Doronzo, M. Moggio, S. Jann and G. Scarlato 659

Monoclonal antibodies against sensory neuron specific antigens define the extent of neuronal abnormality in the *mf* mutant rat. F. Scaravilli, T. M. Jessell, J. Dodd and L. Chimelli 677

Abnormal vibration-induced cerebral blood flow responses in idiopathic dystonia. L. W. Tempel and J. S. Perlmutter 691

A quantitative study of sensory function in hereditary spastic paraplegia. W. Schady and A. Sheard 709

Familial cerebral amyloid angiopathy with nonneuritic amyloid plaque formation. G. T. Plant, T. Révész, R. O. Barnard, A. E. Harding and P. C. Gautier-Smith 721

Troubled letters but not numbers. Domain specific cognitive impairments following focal damage in frontal cortex. S. W. Anderson, A. R. Damasio and H. Damasio 749

Visual control of balance in cerebellar and parkinsonian syndromes. A. M. Bronstein, J. D. Hood, M. A. Gresty and C. Panagi 767

Effects of brainstem lesions on the masseter inhibitory reflex. Functional mechanisms of reflex pathways. B. W. Ongerboer de Visser, G. Cruccu, M. Manfredi and J. H. Th. M. Koelman 781

Synapses, axonal and dendritic patterns of GABA-immunoreactive neurons in human cerebral cortex. Z. F. Kisvárday, A. Gulyas, D. Beroukas, J. B. North, I. W. Chubb and P. Somogyi 793

The bulbocavernosus reflex. A single motor neuron study. D. B. Vodušek and M. Janko 813

Oculomotor disturbances during visual-vestibular interaction in Wallenberg's lateral medullary syndrome. W. Waespe and W. Wichmann 821

Book reviews 847

Announcements 855

Brain (1990), **113**, 581–602

RECENCY AND FREQUENCY DISCRIMINATION IN THE AMNESIC PATIENT H.M.

by H. J. SAGAR,[1,2,3] J. D. E. GABRIELI,[1,2] E. V. SULLIVAN[1,2,3] *and* S. CORKIN[1,2]

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SUMMARY

Temporal contextual memory and event memory were compared across retention intervals in the patient H.M. who is amnesic following bilateral medial temporal lobectomy. Memory for temporal context was assessed using verbal and nonverbal recency discrimination tasks and a frequency task in which subjects made discriminations between words repeated 1, 3 or 5 times. The tests evaluated event memory under parallel conditions by two-choice content recognition tasks. In both recency and frequency tests, H.M. showed above-chance and often normal temporal contextual memory under conditions of impaired and even chance-level content recognition. These results show that temporal contextual memory does not require intact content recognition and is independent of medial temporal lobe structures. Furthermore, the amnesia of bilateral medial temporal lobe resection does not manifest primary loss of temporal contextual memory.

INTRODUCTION

Studies of normal subjects have indicated that information related to the recency and frequency of past events may be processed in memory independently from information related to the content of those events (e.g., Hasher and Zacks, 1979). Evidence for the anatomical substrate of the different cognitive processes has been provided by Milner (1971) and Corsi (1972). In patients treated by focal cortical excision for epilepsy, unilateral temporal lobectomy was associated with mild material-specific memory deficits but preserved recency discrimination, whereas frontal resections resulted in recency discrimination deficits but normal content recognition. These results suggest that recency discrimination is served by the frontal lobes and content recognition by the temporal lobes, although not necessarily exclusively so in either case. Similarly, Smith and Milner (1983, 1988) demonstrated that estimation of frequency of occurrence of nonverbal material is most susceptible to disruption by lesions in the right frontal lobe, whereas only right temporal lobe excisions impaired nonverbal recognition. For verbal material, right frontal, right temporal and left temporal lobe excisions had no effect on

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frequency estimation; cases of left frontal lobectomy were not reported (Milner *et al.*, 1985).

The application of these findings to interpretation of the amnesic syndrome is less clear. In amnesia, the memory deficit is more severe than can be accounted for by the sum of unilateral material-specific memory deficits (Corsi, 1972) and amnesic syndromes may be produced from lesions in a number of brain regions (Corkin *et al.*, 1985). These findings suggest that cognitive processes in amnesic syndromes may not be predictable simply from the results of experiments with patients who have material-specific memory deficits and focal brain lesions. Although cases of unilateral temporal lobectomy showed preserved recency and frequency discrimination, it is unclear whether such performance would remain normal if content recognition were severely impaired, and whether the patterns of deficit in content recognition and discrimination of recency and frequency would differ according to the aetiology of the amnesia and the nature of the memorized material.

Some studies of amnesic syndromes have shown a deficit in recency discrimination (Hirst and Volpe, 1982) or in memory for broad temporospatial context (Huppert and Piercy, 1976) when content recognition was intact. Observations in Korsakoff's syndrome (KS) showed disproportionate impairment in frequency estimation although, in these cases, recall of content was also markedly impaired (Strauss *et al.*, 1985). These studies suggest that the amnesic syndrome may be based upon a selective loss of temporal or temporospatial context. Generalization of these results to all amnesic syndromes is not justifiable, however, for two reasons. First, Squire *et al.* (1981) showed that patients with KS had disproportionate deficits in temporal ordering compared with patient N.A. and patients amnesic from bilateral electroconvulsive therapy; frontal lobe pathology in KS was postulated as the basis of the difference. The mixed group of amnesic patients in the study of Hirst and Volpe (1982) included cases of anterior communicating artery aneurysm rupture, hypoxia and head injury, conditions that are also associated with frontal lobe damage (Blackwood and Corsellis, 1976; Gade, 1982) and that may therefore show disproportionate deficits in temporal ordering. Secondly, the normal content recognition of the patients in both studies did not permit evaluation of the nature of the relative deficit in recency discrimination when content recognition is severely impaired, especially because loss of temporal contextual memory is an early consequence of degraded memory for content, even in normal subjects (Squire *et al.*, 1981). In order to evaluate the generality of the clinicopathological findings of Milner and her colleagues (Milner, 1971; Corsi, 1972; Smith and Milner, 1983, 1988) for severe global amnesia due to circumscribed cerebral pathology, we investigated content recognition and discrimination of recency and frequency in the patient H.M. who became severely amnesic as a result of bilateral temporal lobe resection for epilepsy in 1953 (Scoville and Milner, 1957; Corkin, 1984). Discrimination of recency and frequency and recognition of content were measured under parallel forgetting conditions. In this way, temporal contextual memory was evaluated at all levels of content recognition from normal to chance performance. Partial reports of this study were presented previously (Sagar *et al.*, 1984; Sagar and Sullivan, 1988).

METHODS

Subjects

The participants were the amnesic patient H.M. (Scoville and Milner, 1957; Corkin, 1984) who, at the time of testing, was aged 58 yrs and had had 12 yrs of education, and 10 normal control subjects (mean age 62.8 yrs; mean yrs of education 13.5).

Procedure

Verbal Temporal Ordering (VTO) Test. This test, modified from Hirst and Volpe (1982), consisted of a series of 493 nouns that were displayed on a computer screen at a rate of one every 2 s. Each word contained 4, 5 or 6 letters and had a frequency rating in the English language of 25 times per million or more (Kucera and Francis, 1967). At random intervals throughout the display, one of two types of item appeared on the screen: content recognition tests contained a previously presented word and a foil; recency discrimination tests contained two previously presented words. The test questions 'Which of these words have you seen on this test?' or 'Which of these words did you see more recently?' appeared at the top of the screen and were also spoken by the examiner. The two alternative answers subsequently appeared side-by-side underneath the question on the screen.

The test questions appeared at various intervals after stimulus presentation. The duration of each stimulus-test interval was defined as the number of intervals between events, where an event was either another stimulus word or a test question. For example, where a question immediately followed stimulus presentation, the stimulus-test interval was 1 and there were no intervening events; where a question was the third item after stimulus presentation, the stimulus-test interval was 3 and there were 2 intervening items that could be stimulus words or test questions relating to earlier stimulus words. The position of a content recognition question was defined by one such interval. Recency discrimination questions examined two previously presented words; the position of a recency discrimination question was therefore defined by two intervals, one corresponding to each word examined in the test.

For content recognition, the stimulus-test intervals were 1, 3, 6, 10, 15, 25, 50, 100 and 150; there were 5 exemplars at each position. For recency discrimination, all possible pairings of these stimulus-test intervals were used (1−3, 1−6, 1−10 . . . 50−100, 50−150, 100−150); there were 5 exemplars for each pairing.

Test questions were presented in random order, subsequently modified to equalize the proportion of test questions and single word stimuli within each stimulus-test interval. The 2 words presented as choice responses in each test of content recognition or recency discrimination were matched for word length and frequency. For each stimulus-test interval, the 5 exemplars of each type of test (content recognition or recency discrimination) were matched for word length and frequency to the list as a whole; content recognition and recency discrimination test responses were similarly matched to each other. In the two-choice tests, 50% of the correct responses appeared on the left half of the screen and 50% on the right in random order.

During administration of the test, subjects were seated beside the examiner and in front of the screen. They were instructed to read each word aloud and to remember the words in their order of appearance. Subjects gave oral responses to the questions in unlimited time. The examiner entered the response into the computer at the same time as he instructed the subject 'Keep on reading'. The registration of the response triggered the appearance of the next stimulus word.

In order to increase the number of data points for recognition memory, patient H.M. was given the VTO test on 5 occasions between 4 days and 2 months apart. Three of these tests were given in the form described. The remaining 2 tests were modified to conform more closely to the procedure of Milner (1971) and Corsi (1972). Thus these 2 tests employed one question 'Which of these words did you see more recently?' to test both content recognition and recency discrimination throughout the test. In all other respects, the procedure was identical to that described for the remaining 3 tests. Comparison of performance across the two conditions allowed us to examine directly the effect of the different test procedures on H.M.'s recognition memory and recency discrimination.

Nonverbal Temporal Ordering (NVTO) Test. This test followed the same procedure as VTO but used as stimuli abstract wallpaper designs mounted on 5×8 inch cards. Designs were selected that could not easily be labelled verbally. Subjects sat opposite the examiner and were presented with cards at a rate of one every 2 s. Subjects were instructed to look carefully at the designs and to remember them in their order of appearance. Responses were recorded by hand by the examiner. In all other respects, the test was identical with VTO.

NVTO was given to H.M. on 4 occasions, between 4 days and 2 months apart. Three of these tests were given in the form described. The remaining test employed the one question condition described under VTO.

Verbal Frequency Test. The verbal frequency test consisted of 957 nouns with a frequency rating in the English language of 25 or more (Kucera and Francis, 1967) displayed on a computer screen at a rate of one every 2 s. The word list, comprising equal numbers with 4, 5 and 6 letters, was structured in 33 blocks with 29 words per block. Within each block, 3 words each occurred once, 3 others each 3 times and a further 3 words each 5 times, distributed pseudorandomly through the block. These words formed the stimulus items. The remaining two words were placed at the end of each block as buffer items and were not used as test stimuli. For each frequency of repetition (1, 3 or 5) within each block, there was therefore a triad of different words, each of which formed the item of a subsequent content-recognition or frequency-discrimination test. Two choice word-recognition (content) or frequency-discrimination questions occurred between blocks, sampling words from blocks earlier in the test. Content-recognition tests comprised a previously presented word and a foil; recency-discrimination tests comprised 2 words presented a different number of times (1, 3 or 5) within the same block. The test questions 'Which of these words have you seen on this test?' or 'Which of these words did you see more often?' appeared at the top of the screen and were also spoken by the examiner. Immediately after the question was read by the examiner, the two alternative answers appeared side-by-side underneath the question on the screen.

Separate content-recognition questions examined one word from each triad within each block, thereby sampling words appearing 1, 3 and 5 times. Separate frequency-discrimination questions examined all possible pairings of word frequency (1−3, 1−5, 3−5) within the same block, using the remaining words of each word triad. The words used as stimuli in different blocks were matched for length and frequency in the English language; the two choices of each content-recognition or frequency-discrimination question were similarly matched to each other. The three content-recognition and three frequency-discrimination questions pertaining to a given block were presented sequentially in pseudorandom order at various intervals after stimulus presentation. The stimulus-test interval was defined as the number of 29-word blocks intervening between presentation of a block and the questions relating to that block.

Questions pertaining to the first 17 blocks (early blocks) appeared during presentation of the test at stimulus-test intervals of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 15, 18, 21, 24, 27 and 30. Questions pertaining to the last 16 blocks (late blocks) appeared sequentially at the end of the test in an order corresponding to stimulus-test intervals of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15.

During administration of the test, subjects were seated beside the examiner in front of the screen. They were instructed to read each word out loud and to remember the words and their frequency of occurrence. Subjects gave oral responses to the questions in unlimited time. The examiner entered the response into the computer at the same time as he instructed the subject 'Keep on reading'. The registration of the response triggered the appearance of the next stimulus word.

The verbal frequency test was given to H.M. on 5 occasions over 2 months. Three of these 5 tests were given in the form described. The remaining 2 tests employed one question 'Which of these words did you see more often', to parallel the procedure of the VTO and NVTO tests.

RESULTS

In the analysis of results, normal performance was taken as the range of scores of the normal control group. Except where indicated, the pattern of results was qualitatively identical when the normal range was expressed as 95% confidence limits.

Analysis of results of individual subjects showed variability of performance but no normal control subject achieved scores in content recognition as low as those of H.M. on the first trial. Content recognition and recency discrimination were not correlated in the normal control group (for VTO total scores, $r = 0.09$; NVTO, $r = 0.41$, $P = 0.24$). Thus it was not possible to compare H.M.'s recency discrimination with that predicted from the content recognition scores of the control group. Moreover, H.M.'s performance overlapped that of the normal control subjects. In order to determine systematic differences between H.M.'s performance and that of normal subjects, group statistics were therefore adopted, based upon the scores of the normal control group and the repeated trials of H.M. In this analysis, H.M.'s trials were assumed to be independent for statistical purposes. Although potentially fallacious for a within-subjects analysis, this procedure is acceptable for H.M. for the following reasons. First, the known properties of H.M.'s amnesia render implausible the suggestion that his declarative memory performance would gain from repeated trials often months apart; and secondly, analysis of his performance across trials suggests statistical independence between trials. Analysis of performance on multiple trials showed that H.M.'s performance was variable (e.g., Table 1) but there was no significant improvement across trials (using Friedman's analysis of variance, corrected for ties: for VTO content, $\chi^2 = 9.27$, recency $\chi^2 = 4.95$; for NVTO content, $\chi^2 = 1.33$, recency $= 1.39$). Content recognition on VTO trial 3 was significantly superior to that of both trial 1 (Wilcoxon $Z = 2.41$, $P < 0.02$) and trial 5 ($Z = 2.0$, $P < 0.05$). In order to address the possibility of interaction between trials, however, results are presented for the first trial of each test separately from the results pooled across all trials for each test.

Recency discrimination

Total scores. For the *multiple trials*, H.M.'s performance did not differ between test conditions in which a single recency discrimination question was used to examine content recognition as well as recency discrimination and those in which different questions were used for each type of judgement (Table 2). Accordingly, the results of all 5 tests were pooled for further analyses.

TABLE 1. TOTAL SCORES ON THE VTO AND NVTO TESTS (% CORRECT)

	Control subjects (n = 10)			*H.M.*					
	Mean (and SEM)	*95% confidence interval*	*Range*	*Trial 1*	*Trial 2*	*Trial 3*	*Trial 4*	*Trial 5*	*All trials (mean and SEM)*
VTO									
Content	81.3 (2.25)	65.5–97.2	66.7–91.1	57.8	66.7	86.7	68.9	68.9	69.8 (4.70)
Recency	68.3 (1.56)	57.3–79.3	58.5–77.9	58.9	66.0	62.2	71.2	72.9	66.3 (2.64)
NVTO									
Content	78.7 (2.97)	57.8–99.6	66.2–88.9	62.2	66.7	71.1	62.2	–	65.8 (2.19)
Recency	62.2 (1.09)	54.0–70.4	57.3–69.5	58.3	59.5	62.7	55.6	–	61.1 (1.38)

TABLE 2. TOTAL SCORES ON THE VTO, NVTO AND FREQUENCY TESTS ACCORDING TO NUMBER OF TEST INSTRUCTIONS

	One instruction		*Two instructions*	
	No. of tests	*Mean percentage correct*	*No. of tests*	*Mean percentage correct*
VTO				
Content	2	68	3	71
Recency	2	76	3	73
NVTO				
Content	1	67	3	64
Recency	1	60	3	59
Frequency				
Content	3	54	2	49
Frequency	3	54	2	52

A repeated measures ANOVA of Group×Task examined content and recency judgements (Tasks) in H.M. (Multiple trials) and normal control subjects (Groups) for the VTO and NVTO tests separately. Significant main effects were found for Group and Task on both types of test (for Groups, VTO F(1,1) = 6.03, $P < 0.03$; NVTO F(1,1) = 5.39, $P < 0.05$. For Tasks, VTO F(1,1) = 16.1, $P < 0.002$; NVTO F(1,1) = 43.0, $P < 0.001$). Thus H.M. was significantly impaired in verbal and nonverbal content recognition but was normal in recency discrimination on both types of test (Table 1). The Group×Task interaction was significant on the NVTO test (F(1,1) = 7.42, $P < 0.02$) but not on the VTO test (F(1,1) = 3.29, $P < 0.10$), supporting a disproportionate deficit in nonverbal recognition relative to recency discrimination in H.M. In control subjects, content recognition scores were higher than recency discrimination scores on the VTO and the NVTO test ($P < 0.01$). In H.M., however, content recognition was not superior to recency discrimination on either test (Table 1).

Binomial probabilities of above-chance performance by H.M. were calculated for content and recency scores at each interval on the VTO and NVTO tests. For VTO, H.M. achieved above-chance performance on content at intervals of 1 ($P < 0.001$), 3 ($P < 0.01$) and 15 ($P < 0.02$) and, on recency, at 1, 3, 6 and 10 ($P < 0.001$). For NVTO, he achieved above-chance performance for content at 1 ($P < 0.002$) and 15 ($P < 0.01$) and for recency at 1 ($P < 0.001$) and 6 ($P < 0.01$). Using the strict Bonferroni correction for multiple analysis, significance was defined as $P < 0.003$ for the 17 analyses of each test. By these criteria, H.M. achieved above-chance performance on VTO recency discrimination at stimulus-test intervals of 1, 3, 6 and 10 but on content recognition at only 1. For NVTO, he achieved above-chance recency discrimination and content recognition at an interval of 1 but was at chance at all other intervals. The results on the VTO test indicate that H.M. is able to achieve above chance performance on recency discrimination when his corresponding content recognition is at chance levels.

On the *first trial* of each test, H.M.'s total scores on recency discrimination were normal, despite impaired content recognition in both types of test. When the normal range was expressed as 95% confidence limits, H.M.'s performance on verbal content recognition remained abnormal, but his scores on verbal recency discrimination and on both the nonverbal tasks fell within the normal range (Table 1).

Effect of interval. For the analysis of *multiple trials*, repeated measures ANOVA of Group×Interval were performed separately for content recognition and recency discrimination on the VTO and NVTO tests. Significant main effects were found for Group on verbal ($F(1,8) = 6.45$, $P < 0.025$) and nonverbal content recognition ($F(1,8) = 6.96$, $P < 0.025$) but not on verbal ($F(1,7) = 0.50$, $P = 0.49$) or nonverbal recency discrimination ($F(1,7) = 2.47$, $P = 0.14$). Significant main effects were found for Interval on verbal content recognition ($F(1,8) = 6.31$, $P < 0.001$), and verbal ($F(1,7) = 26.7$, $P < 0.001$) and nonverbal recency discrimination ($F(1,7) = 7.76$, $P < 0.001$) but not on nonverbal content recognition ($F(1,7) = 1.06$, $P = 0.40$). The Group×Interval interaction was significant only for nonverbal content recognition ($F(1,8) = 2.69$, $P = 0.01$) (Table 3; figs 1, 2).

These analyses reflect deficits in content recognition, but not recency discrimination in H.M. Moreover, nonverbal content recognition differed qualitatively in its relationship

TABLE 3. SCORES AT EACH STIMULUS-TEST INTERVAL ON THE VTO AND NVTO TESTS*

	1	*3*	*6*	*10*	*15*	*25*	*50*	*100*	*150*
VTO									
Content									
Control	100	98	88	76	84	74	78	68	66
	(0)	(2.0)	(5.3)	(7.2)	(6.5)	(7.9)	(5.5)	(8.0)	(7.3)
H.M.									
1st test	100	80	20	40	60	40	60	60	60
All tests	100	76	68	68	72	60	68	68	48
Recency									
Control	96.6	82.7	69.6	66.4	56.5	58.6	58.0	58.0	–
	(0.8)	(3.0)	(2.2)	(2.8)	(3.0)	(4.1)	(4.4)	(7.0)	
H.M.									
1st test	100	83	63	60	55	40	30	40	–
All tests	99	88	69	71	55	47	42	60	–
NVTO									
Content									
Control	78	68	80	90	76	84	80	84	68
	(7.0)	(8.0)	(6.0)	(4.5)	(4.0)	(6.5)	(5.2)	(5.0)	(5.3)
H.M.									
1st test	80	100	60	60	80	60	60	40	20
All tests	85	70	65	50	80	60	70	50	60
Recency									
Control	77.4	60.9	63.6	62.0	62.5	70.5	46.0	54.0	–
	(3.0)	(2.4)	(2.9)	(3.5)	(2.7)	(3.6)	(4.3)	(6.7)	
H.M.									
1st test	75	51	57	48	65	40	50	80	–
All tests	82	56	61	50	54	55	45	70	–

* Mean percentage correct and, in brackets, SEM. For recency discrimination, scores where pooled according to the position of the more recent items of the stimulus pairs; stimulus-test interval defines this position.

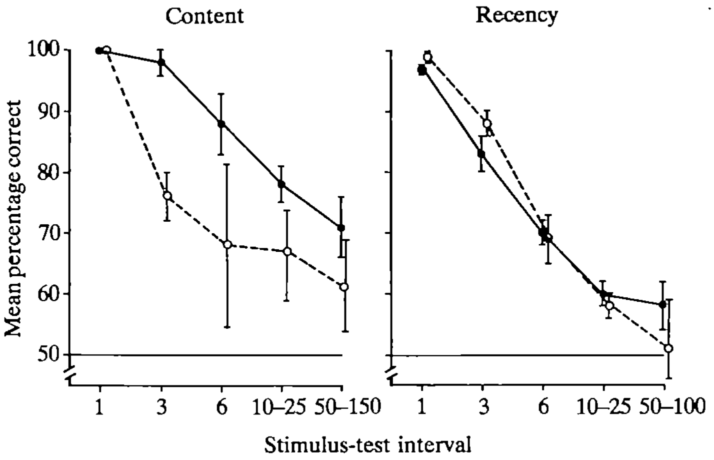

FIG. 1. Mean percentage correct for H.M. (across 5 tests) and control subjects (n = 10) related to stimulus-test interval on the VTO test. For recency discrimination, scores were pooled according to the position of the more recent items of the stimulus pairs; stimulus-test interval defines this position. Vertical bars denote SEM. H.M. showed normal recency discrimination but impaired content recognition. Broken line and open circles = H.M. Continuous line and closed circles = controls.

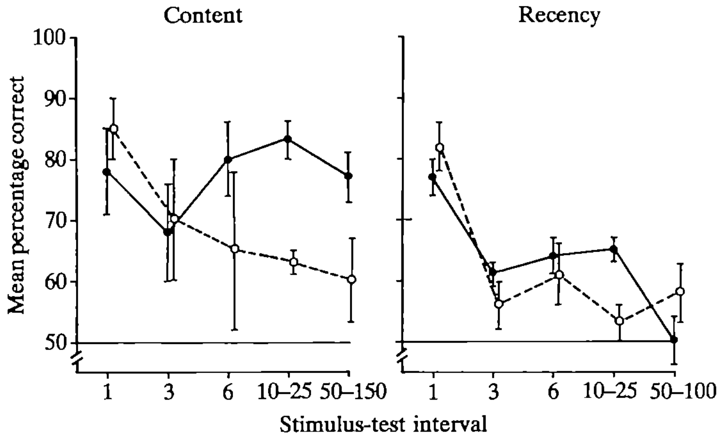

FIG. 2. Mean percentage correct for H.M. (across 4 tests) and control subjects (n = 10) related to stimulus-test interval on the NVTO test. For recency discrimination, scores were pooled according to the position of the more recent items of the stimulus pairs; stimulus-test interval defines this position. Vertical bars denote SEM. H.M. showed normal recency discrimination but impaired content recognition. Symbols as in fig. 1.

with stimulus-test interval from verbal content recognition or verbal and nonverbal recency discrimination (fig. 2).

In content recognition, control subjects showed different forgetting curves for verbal and nonverbal material despite similar total scores in both tests. Content recognition of verbal material followed a classical forgetting function; performance declined acutely as the stimulus-test interval increased (fig. 1). For nonverbal material, however, the function was 'flat'; performance at longer stimulus-test intervals was similar to that at shorter stimulus-test intervals (fig. 2). In control subjects, forgetting curves for verbal and nonverbal recency discrimination were qualitatively similar to each other but steeper than the corresponding curves for content recognition. Thus, for both classes of material, performance in recency discrimination declined more abruptly with increasing stimulus-test interval than did content recognition.

On the *first trial*, H.M.'s performance was qualitatively similar to his results from the pooled trials (Table 3). Thus H.M. resembled control subjects in showing inferior content recognition and recency discrimination at longer stimulus-test intervals than at shorter intervals, but the patterns of performance for content recognition and recency discrimination differed qualitatively from each other. In the VTO test, the forgetting curve of content recognition by H.M. was much steeper than that of control subjects, such that his performance at a stimulus-test interval of 3 was at the lowest limit of the normal range, and at a stimulus-test interval of 6 or more had fallen well outside the normal range to change levels (Table 3). For verbal recency discrimination, by contrast, the forgetting curve for H.M. mirrored much more closely that of control subjects: his performance was normal at all stimulus-test intervals, and he achieved above-chance performance up to stimulus-test intervals of 10 or more. At stimulus-test intervals of 3 and 6, H.M.'s recency discrimination was superior to his content recognition, a pattern that was the reverse of that found in control subjects. A similar pattern of performance was seen in H.M.'s results on the NVTO test (Table 3). Despite chance performance on content recognition at longer stimulus-test intervals, H.M.'s performance on recency discrimination was normal throughout, including the longer intervals where, unlike control subjects, his performance in recency discrimination was superior to his recognition of content.

When the normal ranges were expressed at 95% confidence intervals, H.M.'s content recognition on the VTO test at a stimulus-test interval of 3 was clearly below the lower limit of normal, but the remaining results were qualitatively identical.

In summary, (1) H.M. achieved normal verbal and nonverbal recency discrimination under conditions of impaired content recognition; (2) he showed above-chance performance on verbal recency discrimination when content recognition, examined under parallel conditions, was at chance level; and (3) for nonverbal material, a significant Group × Task interaction indicated a disproportionate impairment in content recognition relative to recency discrimination by H.M.

Frequency discrimination

Total scores. For the *multiple trials*, H.M.'s performance did not differ between test conditions in which a single frequency discrimination question was used to examine content recognition as well as frequency discrimination and those in which different questions were used for each type of judgement (Table 2). Accordingly, the results of all 5 tests were pooled for further analysis (Table 4). A repeated measures ANOVA of Group × Task examined content and frequency judgements (Tasks) in H.M. (Multiple trials) and normal control subjects (Groups) for the early and late blocks separately.

TABLE 4. TOTAL SCORES ON THE FREQUENCY TEST

	Control subjects (n = 10)			*H.M.*					
	Mean (%)	*95% confidence intervals (%)*	*Range (%)*	*Trial 1*	*Trial 2*	*Trial 3*	*Trial 4*	*Trial 5*	*All trials (Mean and SEM)*
Early blocks									
Content	84.9 (1.85)	71.9–97.9	76.5–92.2	51.0	58.8	51.0	49.0	56.9	53.3 (1.90)
Frequency	68.4 (1.61)	57.0–79.8	60.8–74.5	47.1	54.9	54.9	58.8	54.9	54.1 (1.91)
Late blocks									
Content	75.4 (3.10)	52.9–97.9	56.3–85.4	56.3	35.4	60.4	50.0	47.9	50.0 (4.27)
Frequency	52.7 (1.86)	39.6–65.8	41.7–60.4	64.6	50.0	47.9	43.8	52.1	51.7 (3.51)

Significant main effects were found for Group and Task under both conditions (for Group, early blocks $F(1,1) = 113$, $P < 0.001$; late blocks $F(1,1) = 10.8$, $P < 0.01$; for Task, early blocks $F(1,1) = 53.1$; late blocks, $F(1,1) = 48.4$, $P < 0.001$). Thus H.M. was significantly impaired in content recognition and frequency discrimination under both conditions. The Group×Task interaction was significant on the early blocks ($F(1,1) = 30.2$) and the late blocks ($F(1,1) = 30.1$, $P < 0.001$). Inspection of the total scores, however, indicates that this interaction is a likely floor effect due to overall chance performance by H.M. on both content and frequency judgement (Table 4).

The scores of healthy control subjects in content recognition and frequency discrimination were lower for the late blocks than for the early blocks ($P < 0.01$, Table 4). This decline in performance of control subjects from early to late blocks was more marked for frequency discrimination (mean 15.7% decline) than for content recognition (mean 9.5% decline). In early and in late blocks, the performance of control subjects in content recognition was superior to that in frequency discrimination ($P < 0.01$). In both the early and late blocks, H.M. achieved total scores at or near chance performance on content recognition and frequency discrimination, which did not differ from each other.

On the *first trial*, in contrast to the pattern in control subjects, H.M.'s performance in the late blocks improved relative to the early blocks in content recognition and in frequency discrimination. For content recognition, his score rose from chance levels on the early blocks, well below the lower limits of the normal range, to the lower limits of the normal range on the late blocks. For frequency discrimination, his improvement from the early to the late blocks was more marked: his performance rose from chance levels on the early blocks to the upper limits of the normal range on the late blocks. Moreover, in contrast to the pattern of performance of control subjects, his frequency discrimination was superior to his content recognition on the late blocks (Table 4).

Effect of interval. For the analysis of *multiple trials* (fig. 3), repeated measures ANOVA of Group×Interval were performed separately for content recognition and frequency discrimination on the early and late blocks. Significant main effects were found for Group

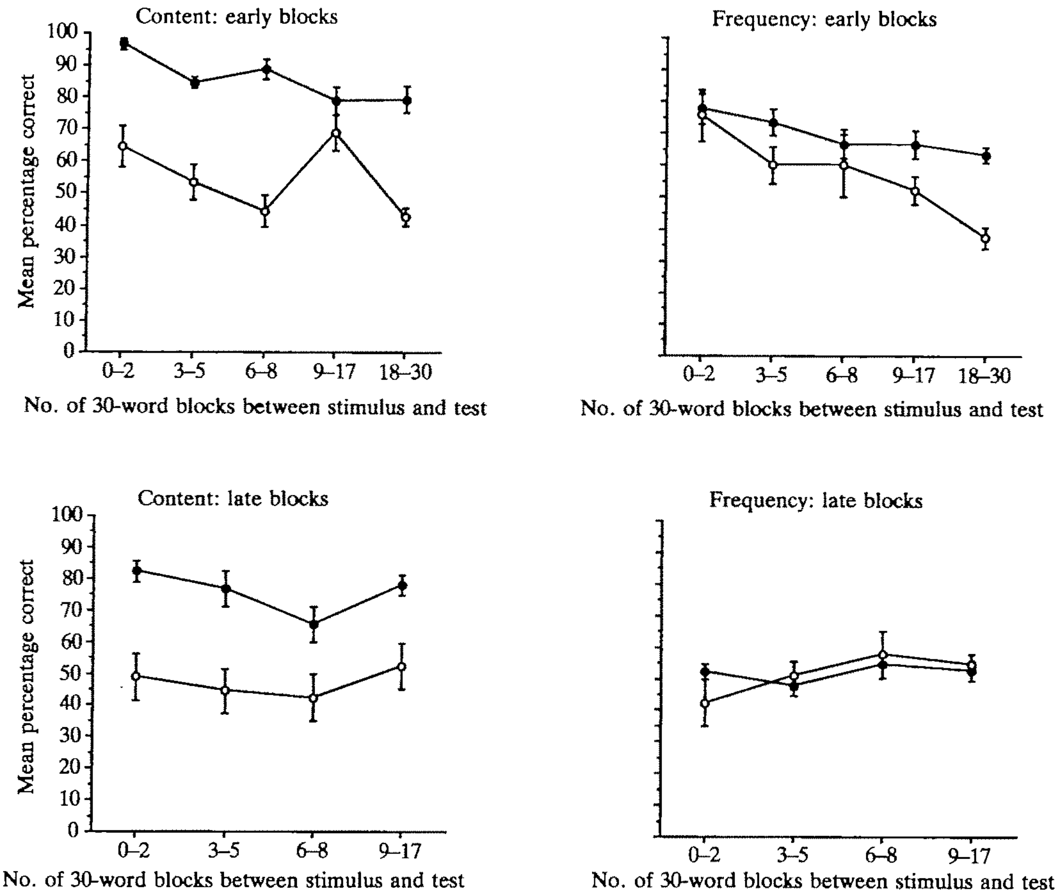

FIG. 3. Scores (mean % correct) for H.M. (across 5 tests) and control subjects (n = 10) related to retention interval for the early and late blocks of the Frequency test. Vertical bars denote the ranges of control scores. Over the first 8 blocks, H.M.'s frequency discrimination was not significantly impaired whereas content recognition was markedly defective. Open circles = H.M., closed circles = controls.

in content recognition on the early ($F(1,4) = 117$, $P < 0.001$) and the late blocks ($F(1,3) = 39.4$, $P < 0.001$) and for frequency discrimination on the early ($F(1,4) = 17.2$, $P < 0.002$), but not the late blocks. Significant main effects for Interval were found for content recognition ($F(1,4) = 6.29$, $P < 0.001$) and frequency discrimination ($F(1,4) = 5.32$, $P < 0.002$) on the early but not the late blocks. The lack of significance in some analyses of data from the late blocks may be due to a floor effect in performance on frequency discrimination (fig. 3).

On the early blocks, the interaction Group × Interval was significant for content recognition ($F(1,4) = 5.01$, $P < 0.002$) but not frequency discrimination ($F(1,4) = 1.40$, $P = 0.25$). No interactions were significant for the late blocks.

Because of the floor effects on the late blocks, all further analyses were confined to the early blocks. One-way ANOVA were used to compare the performance of H.M.

and normal control subjects at each stimulus-test interval. For content recognition, H.M. showed impaired performance at intervals of 0–2, 3–5, 6–8 and 18–30 ($P < 0.001$) but not 9–17 ($P = 0.18$). For frequency discrimination, by contrast, he was impaired at the longest interval, 18–30 ($P < 0.001$) but not at any of the shorter intervals, 0–2 ($P = 0.80$), 3–5 ($P = 0.08$), 6–8 ($P = 0.49$), 9–17 ($P = 0.06$). Over the first 8 blocks, but not beyond, he scored above chance on frequency discrimination (binomial probability, $P < 0.005$) but not content recognition. Thus where his frequency performance was above chance levels (intervals 0–8) he performed normally on frequency discrimination despite chance performance in content recognition. This finding was confirmed in a Group×Interval ANOVA for the first 8 blocks which showed significant Group effects for content recognition ($F(1,2) = 130$, $P < 0.001$) but not for frequency discrimination ($F(1,2) = 2.29$, $P = 0.15$). Moreover, the ANOVA Group×Task for the first 8 blocks showed a significant interaction ($F(1,1) = 30.8$; $P < 0.001$); unlike the significant Group×Task interaction on the total scores, this result is unlikely to be an artefact due to floor effects in performance.

On the *first trial* in the early and in the late blocks, content recognition and frequency discrimination by control subjects declined as the stimulus-test interval increased except frequency discrimination in the late blocks, which was at chance performance levels at all stimulus-test intervals (fig. 4).

In the early blocks, content recognition by H.M. was at or around chance levels at all stimulus-test intervals. By contrast, frequency discrimination over the first 3 blocks was well above chance performance and towards the upper part of the normal range of scores. With increasing stimulus-test intervals, his frequency discrimination in the early blocks dropped abruptly to chance levels. In the late blocks, his content recognition was again at chance levels at all stimulus-test intervals but frequency discrimination remained above chance levels at all stimulus-test intervals. In contrast to content recognition on which, in general, he scored below or in the lower part of the normal range, his frequency discrimination was above or in the upper part of the normal range of scores at all stimulus-test intervals.

The high scores of H.M. on frequency discrimination are unlikely to result from chance alone. Binomial probability analysis indicates that his frequency discrimination on the late blocks is significantly above chance performance ($P < 0.05$) whereas content recognition is at chance levels ($P = 0.24$).

Effect of item repetition. For the *multiple trials* (fig. 5) content recognition for items repeated 1, 3 or 5 times was compared between H.M. and normal control subjects using repeated measures ANOVA of Group×Repetition. In the early blocks, main effects were found for Group ($F(1,2) = 114$, $P < 0.001$) and Repetition ($F(1,2) = 5.47$, $P = 0.01$) with no interaction ($P = 0.10$). In the late blocks, there were significant Group effects ($F(1,2) = 23.3$, $P < 0.001$) but no significant repetition effects or interaction, possibly due to floor effects in performance. Content recognition on the early blocks was better for items repeated 3 or 5 times than for items viewed only once, and normal control subjects performed better than did H.M.

Frequency discrimination of 1 vs 3, 1 vs 5 and 3 vs 5 repeated items was compared

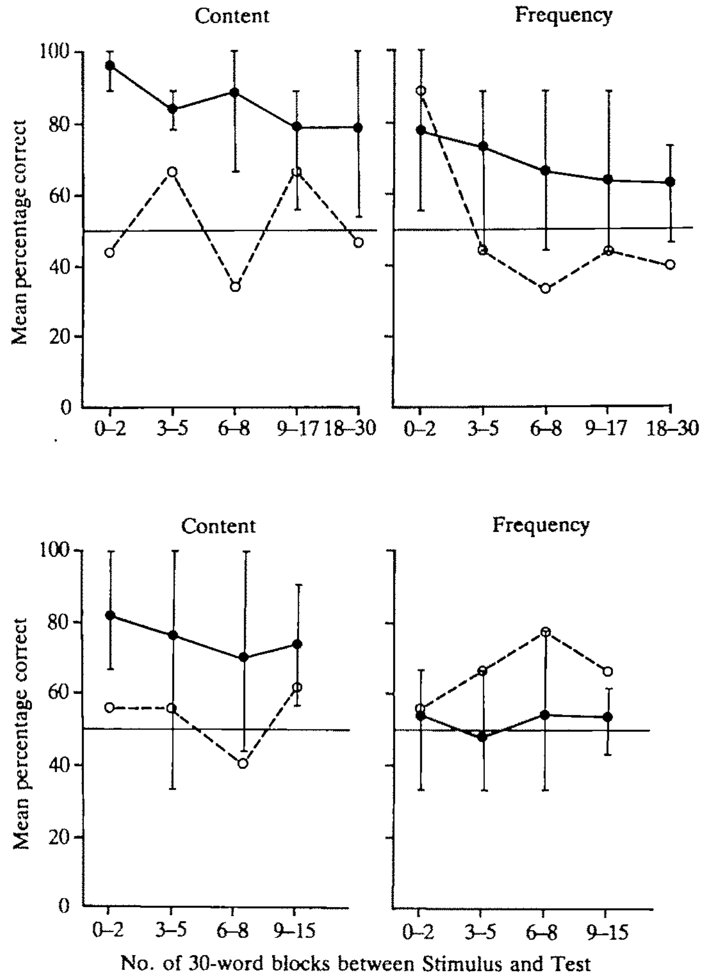

FIG. 4. Scores (mean % correct) for H.M. and control subjects (n = 10) related to retention interval for the early (top row) and late (bottom row) blocks of the Frequency test (first trial). Vertical bars denote the ranges of control scores. In the late blocks, H.M.'s content recognition was at chance levels but his frequency discrimination was significantly above chance and approaching the level of the best control subject. Symbols as in fig. 1.

between H.M. and normal control subjects using an ANOVA of Group×Repetition (1 vs 3, 1 vs 5, 3 vs 5). In the early blocks, main effects were found for Group ($F(1,2) = 28.8$, $P < 0.001$) and Repetition ($F(1,2) = 8.18$, $P < 0.002$) with no interaction. No significant effects were found for performance on the late blocks, possibly due to floor effects in performance. Discrimination of 3 vs 5 repetitions was inferior to 1 vs 3 and 1 vs 5 discriminations and H.M. performed inferiorly to normal control subjects.

On the *first trial*, frequency discrimination by H.M. was, in general, best for 1 vs 3 repeated items. In the early blocks 1 vs 3 frequency discrimination was well into the normal range, whereas content recognition for once and thrice-repeated items was below

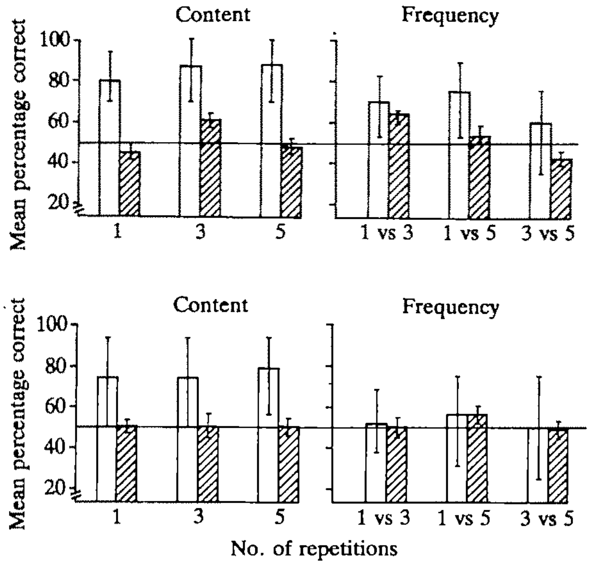

FIG. 5. Scores (mean % correct) for H.M. (across 5 tests) and control subjects related to the number of repetitions of stimulus words in the early (top) and late (bottom) blocks of the Frequency test. Vertical bars denote the ranges of control scores. Open areas = controls (n = 10); hatched areas = H.M.

the lower limit of the normal range and inferior to his 1 vs 3 frequency discrimination. Similarly, in the late blocks, 1 vs 3 frequency discrimination by H.M. was at the upper limit of the normal range and superior to his content recognition of once or thrice-repeated items, which were both towards the lower part of the normal range, approaching chance levels of performance. In the late blocks, 1 vs 5 and 3 vs 5 frequency discriminations by H.M. were also in the upper part of the normal range, and in both cases his performance was superior to his content recognition of words repeated 1, 3 or 5 times.

In summary, (1) H.M. showed above-chance frequency discrimination when content recognition was at chance levels; (2) under some circumstances, he showed normal frequency discrimination with impaired content recognition; (3) when his frequency discrimination was above chance performance, the scores were superior to his content recognition under equivalent conditions. This pattern was the reverse of that found in the control group; (4) content recognition and frequency discrimination by normal subjects declined from early to late blocks, but, on the first trial, H.M.'s performance improved.

DISCUSSION

The principal finding of this study was that amnesia due to bilateral medial temporal lobe resection is associated with relatively preserved judgements of recency and frequency despite severe impairment in classical recognition memory, namely memory for the content of past events or facts. Thus, on the temporal ordering and frequency discrimination tasks, H.M. sometimes showed normal, above-chance performance on the recency and frequency items under conditions of impaired, chance-level content recognition. His scores on recency discrimination were similar to his content recognition despite observations on control subjects that identify recency discrimination as the more difficult task. Moreover, unlike control subjects, his performance on frequency discrimination was often *superior* to his content recognition. Despite the evident variability of H.M.'s performance, it is unlikely that the observed differences between his content recognition and judgements of recency and frequency result from chance alone for the following reasons. First, the analyses are based upon multiple test administrations to H.M. which, in our present state of knowledge, can be assumed to be independent of each other. Secondly, the marked decline in his content recognition at stimulus-test intervals beyond immediate memory conforms to the known properties of his amnesic syndrome (Milner, 1962; Corkin, 1984; Corkin *et al.*, 1985). Thirdly, his preserved verbal recency discrimination at stimulus-test intervals of 1, 3, 6 and 10 each represents the mean of 125–200 observations and is unlikely to result from chance alone ($P < 0.001$). Fourthly, H.M. scored above chance on frequency discrimination on the early blocks 0–8 (mean 65.2%) but was at chance performance on content recognition throughout. The observations on frequency discrimination and in content recognition on these blocks across 5 trials amounted to 135, so the experimental results are unlikely to be due to chance alone ($P < 0.002$).

Two conclusions can be drawn from these results. First, the findings of Milner (1971) and Corsi (1972) that unilateral temporal lobe lesions produce impaired content recognition with preserved recency discrimination apply also to bilateral temporal lobe lesions in which content recognition is much more severely impaired. Our findings suggest that cognitive processes serving recency and frequency discrimination may function independently of those involved in content recognition and depend on the integrity of different brain regions. Secondly, hypotheses of amnesia based upon specific loss of temporal contextual memory do not have general application and, specifically, do not explain the amnesia associated with bilateral medial temporal lobe lesions.

Cognitive processes involved in temporal judgements

Several models have been proposed to describe the cognitive capacities involved in temporal order judgement (Friedman and Wilkins, 1985). Some models are based on access to temporal information in memory: indirectly, from the sequence of storage or trace-strength of the memorized material (Hinrichs, 1970), or directly from temporal-order information that is encoded independently from information related to the content of the memorized material (Tulving and Madigan, 1970; Tzeng and Cotton, 1980; Zacks *et al.*, 1984). Other models invoke a higher order system in which temporal judgements are made through a cognitive sequencing process or by a mechanism that discriminates two independently encoded items, temporal or otherwise (Milner, 1971, 1974; Warrington and Weiskrantz, 1982; Warrington, 1985; Sagar and Sullivan, 1988; Sagar *et al.*, 1988*a*, *b*). Evidence for the existence of a temporal ordering system distinct from processes involved in memory for facts has been deduced in normal subjects from the differential effects on test performance of change in the learning strategy. Thus performance on tasks of memory for content information is better when subjects are given prior instructions to learn the test material (intentional learning) than when learning takes place incidentally to some other task, such as reading (Hasher and Zacks, 1979). Recency discrimination, however, does not benefit from such a shift in learning strategy. Similar evidence has been claimed to support the notion of automatic encoding of information related to frequency of occurrence (Zacks *et al.*, 1982).

In our study, the preservation of recency and frequency discrimination under circumstances of impaired content recognition supports the view that temporal judgements are not made from stored information related to the content of memorized material, such as trace strength. The concept of automatic encoding, however, raises certain predictions that are not fulfilled by all the results of this study. Specifically, automatic encoding implies that learning would be unaffected by factors, such as motivation and stress, that influence cognitive capacity and would not be improved by training (Zacks *et al.*, 1984). In our frequency-discrimination test, the performance of normal subjects on content recognition and on frequency discrimination declined from the early to the late blocks. Although there are differences in the test format between the early and the late blocks, it is improbable that these differences could account entirely for the decline in performance of normal subjects; this group achieved a mean score in frequency discrimination of 63.3% at stimulus-test intervals of 18–30 on the early blocks, but performance fell to chance levels at all intervals on the late blocks. These results cannot be attributed to waning attention because subjects were required to read each word aloud throughout the test. Because the test duration was in excess of 1 h, it is likely that the main contribution to this alteration in performance was fatigue, which affected content recognition and frequency discrimination approximately equally. These results are incompatible with the automatic encoding of frequency information which is assumed to require minimal processing capacity (Hasher and Zacks, 1979; Zacks *et al.*, 1982).

Across the 5 trials, H.M. also showed fatigue effects in content recognition and frequency discrimination. On the first trial, however, the results were qualitatively different: he did not show the same fatigue effect in frequency discrimination on the late blocks as did control subjects and his scores were, in fact, superior to those of the early blocks. His correct frequency discrimination on the late blocks of 64.6% was the mean of 48 observations and is unlikely to result from chance alone. Moreover, his best frequency performance (on the late blocks) was comparable to the best performance of control subjects at 68.4% (on the early blocks) yet the corresponding performance for content recognition was markedly inferior (56.3% for H.M. late blocks; 84.9% for control subjects, early blocks; Table 3). Thus the difference in performance of H.M. and control subjects in frequency estimation on the late blocks suggests that fatigue may impair frequency judgements in normal subjects but not always in H.M. One mechanism by which this may occur is that normal subjects preferentially employ effortful processing in frequency judgements, particularly when instructed to remember frequency as in this study, whereas H.M. sometimes uses automatic processing.

Although H.M. showed preservation of temporal contextual memory relative to recognition memory, he certainly did not perform normally on the temporal contextual tasks under all conditions. On frequency estimation, his scores at the longer intervals on the early blocks were clearly abnormal. On verbal recency discrimination, differences from controls at longer intervals may be masked by floor effects in the control group; some normal subjects scored above chance performance at intervals of 25 – 150 whereas H.M. did not. These observations suggest some interdependency between processes serving content memory and those concerned with temporal context. This lack of complete independence between content and context memory does not, however, invalidate the results suggesting separate systems for these two classes of information.

Deutsch (1984) has suggested two complementary mechanisms for making temporal judgement, one based on summation of memory traces and one based on comparison between traces. Although he does not propose specific anatomical sites for these systems, the comparator may be frontally based and involve mediation, whereas the other may be more factually represented and be based on the limbic-diencephalic system. Lesions in either system may impair temporal contextual memory but, with limbic-diencephalic lesions, content memory is much more severely affected. With frontal lesions, the reverse pattern occurs and lesions in both systems, as in Korsakoff's syndrome, produce severe amnesia for both content and temporal context. Our results in H.M. are compatible with this hypothesis. Moreover, although speculative, the results of this study support a dual processing model of temporal contextual memory incorporating automatic/effortful and implicit/explicit distinctions in memory processing (Schacter, 1987): one system is explicit, effortful, declarative and served largely by the limbic-diencephalic system; the other is automatic and served by a cognitive mediational system based on the frontal lobes. This automatic system, which is preserved in H.M., could also be explicit memory but is perhaps more likely to be a component of implicit memory which is known to be preserved in amnesia (Schacter, 1987).

Temporal contextual memory in amnesic syndromes

The cardinal feature of the cognitive performance of an amnesic subject is failure of memory for past events whereas awareness of social skills, language and rules is, in general, preserved (Whitty and Lishman, 1966; Milner, 1982; Warrington and Weiskrantz, 1982; Corkin *et al.*, 1985). This observation has led to attempts to explain the poor performance of amnesic patients as a deficit in cognitive processes that are especially involved with temporal specificity. In normal subjects, memory processes concerned with autobiographical events specific to time and place (episodic memory) have been distinguished from those concerned with rules, language and world knowledge poorly defined by temporospatial context (semantic memory) (Tulving, 1972). According to one view, amnesia comprises a selective loss of episodic memory (Kinsbourne and Wood, 1975, 1982; Parkin, 1982; Schacter and Tulving, 1982*a*, *b*; Warrington and Weiskrantz, 1982; Wood *et al.*, 1982). More specific theories of amnesia have been based on a loss of encoding of information related to the time (Williams and Zangwill, 1950; Whitty and Lewin, 1960; Winocur and Kinsbourne, 1978; Hirst and Volpe, 1982) or temporospatial context (Huppert and Piercy, 1976) of past events, such that amnesic patients have difficulty in distinguishing the content of one past event from another.

Evidence to support these views of amnesia has been derived from studies in which amnesic subjects were shown to fail specifically on temporospatial judgements. Thus, for example, amnesic patients failed to recognize in which environmental setting they had viewed a series of pictorial stimuli despite adequate recognition of the pictures themselves (Huppert and Piercy, 1976). In another study, amnesic subjects were unable to make normal judgements of recency between two stimuli but showed unimpaired recognition of the stimuli themselves (Hirst and Volpe, 1982).

The results of our study show that loss of temporal contextual memory, insofar as it is measured by judgements of recency and frequency, is not a *necessary* accompaniment of severe global amnesia. Three possible explanations may underlie the difference in results between this study and those purporting to support temporal or temporospatial theories of amnesia.

First, recency judgements may be made in different ways according to the severity of the recognition deficit. Thus, for example, loss of temporal contextual memory in patients with mild impairment of content memory may simply be a reflection of degraded normal memory and not a special feature of amnesia (Squire *et al.*, 1981). The severity of impairment in content recognition by H.M. in our study was greater than that of the patients described by Huppert and Piercy (1976) or Hirst and Volpe (1982), at least as measured by the tests used. However, the performance of temporal contextual memory under conditions of severe amnesia may be *qualitatively* different from that of normal degraded memory or mild impairment in memory for content; strength of explicit memory traces may be the dominant mechanism when recognition is only mildly impaired but a separate system, implicit or automatic, may be invoked when recognition is severely disrupted.

Secondly, relative performance in content recognition and recency discrimination by amnesic patients may differ according to the aetiology of the amnesic syndrome. The studies of Squire *et al.* (1981) have shown that patients with Korsakoff's syndrome show a disproportionate difficulty in temporal ordering when compared with patient N.A. or patients treated with bilateral electroconvulsive therapy whose performance in content recognition did not suffer from those with Korsakoff's syndrome. Meudell *et al.* (1985) also found that recency discrimination in this syndrome was poorer than could be accounted for by impaired content memory when performance was compared with degraded memory of normal subjects. Studies by Milner and colleagues demonstrated that patients with frontal lobe resections showed impaired recency discrimination but normal content recognition; patients with unilateral temporal lobectomy, by contrast, showed normal recency discrimination but mild material-specific memory deficits (Milner 1971, 1974; Corsi, 1972). In studies of source amnesia, Schacter *et al.* (1984) have shown that poor recall or recognition of the source of learning, with unimpaired memory for the content of the learning episode, correlates with impaired performance on tests traditionally associated with frontal lobe dysfunction. Patients with Parkinson's disease, who show behavioural (Lees and Smith, 1983) and neurophysiological (Bès *et al.*, 1983; Wolfson *et al.*, 1985) evidence of frontal lobe dysfunction, were selectively impaired in recency discrimination using the VTO test of the study reported here (Sagar *et al.*, 1985, 1988*b*). These findings, in combination with behavioural (Squire, 1982, Moscovitch, 1982) and neuropathological (Lishman, 1981; Victor *et al.*, 1971) evidence of frontal lobe dysfunction in Korsakoff's syndrome, suggest that specific temporal-ordering deficits in amnesia may be more frequent in those patients who have frontal lobe deficits (Mayes *et al.*, 1985).

Recently, Bowers *et al.* (1988) demonstrated impaired acquisition of temporal information in a patient whose amnesia was caused by a focal left retrosplenial lesion; no frontal lobe pathology was evident in vivo. This study indicates that temporal information processing may not depend exclusively on frontal lobe function but may nevertheless be independent of event memory and depend upon different brain regions. Our study adds further weight to this evidence in showing that pure bilateral temporal lobe lesions may produce severe amnesia for content with relative preservation of recency and frequency judgements.

Thirdly, the deficits in event memory in amnesic syndromes may, in some cases, involve impairment in processes concerned with time-tagged information. In our study, recency and frequency discriminations were not only less impaired in H.M. than was recognition of content but were also superior to content recognition, even when content recognition fell to chance levels of performance. Insofar as recency and frequency judgements involve discriminations between two or more independently encoded learning episodes, this result implies that information from each episode is processed in parallel in cognitive processes serving content recognition and temporal discrimination. Because, in both systems, this information relates to discrete learning episodes, it may carry specific time-tags. The function of these time-tags, however, differs between systems. In the system serving content recognition, the time-tags serve to identify each learning episode as a separate event, whereas, in the temporal discrimination system, the time-tags are used in formulating judgements between two or more such episodes. Assuming content recognition, as measured in our study, and event memory reflect functions of the same cognitive processes, the special deficits of temporal lobe amnesic patients in event memory may stem from loss of time-tagged information in content recognition processes but not in temporal discrimination processes.

Warrington and Weiskrantz have proposed that amnesia results from a disconnection between semantic memory processes served by the temporal lobes and a cognitive mediational memory system served by the frontal lobes (Warrington and Weiskrantz, 1982; Warrington, 1985). Memoranda organized by visual imagery, the formation of associative links, semantic schemata and other cognitive mapping are believed to be encompassed by the cognitive mediational system. Because temporal discrimination involves comparative judgements between stimuli encoded independently, the preservation of those temporal discriminations in the amnesia of bilateral temporal lobe resection would be compatible with the existence of such a system. Furthermore, the selective failure of content recognition in H.M. may arise from disconnection between a cognitive mediational system and processes serving content recognition. The preservation of temporal discrimination despite disconnection, however, implies that such a cognitive mediational system has inputs that bypass this disconnection.

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EFFECTIVENESS OF DIFFERENT TASK PARADIGMS IN REVEALING BLINDSIGHT

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SUMMARY

Four patients with hemianopia from posterior cerebral artery infarction were tested for residual unconscious vision ('blindsight') in their anopic hemifield. One task tested for spatial summation between the normal and the abnormal hemifields. A second task tested for temporal interactions between the two hemifields. A third task required a manual localization of the site of a brief flash in the hemianopic side. The last test was administered either in a condition of free gaze during pointing or in a condition in which the gaze was kept fixed throughout all phases of the task. The first two tasks differed from the third not only in the type of visual function, that is, detection vs spatial localization, but also in the response criterion. A forced-choice procedure was adopted in the localization task while in the spatial and temporal interfield interaction tasks a reaction time paradigm that did not require guessing was used. One patient showed unequivocal evidence of blindsight on all tasks, thus excluding the possibility that his blindsight depended on the nature of the response. An interesting dissociation was found in the localization task where 1 patient showed evidence of blindsight when tested under conditions of unrestrained gaze during pointing but not when tested under fixed gaze conditions.

INTRODUCTION

In the last 15 years various studies have shown that some patients with damage to the geniculocalcarine pathway retain some kind of visual function within their perimetrically-defined visual field defect (*see* Weiskrantz, 1986, for review).

Visual detection of flashing stationary (Barbur *et al.*, 1980; Stoerig *et al.*, 1985) or moving targets (Barbur *et al.*, 1980; Blythe *et al.*, 1987) and visual localization by eye and hand movements (Pöppel *et al.*, 1973; Weiskrantz *et al.*, 1974; Perenin and Jeannerod, 1978; Blythe *et al.*, 1987) are by far the most frequent residual capacities described in the literature. However, many other visual abilities such as monocular/binocular discrimination (Richards, 1973), orientation discrimination (Weiskrantz, 1987), resetting of visual threshold (Singer *et al.*, 1977), figure completion (Torjussen, 1978), semantic priming (Marcel, 1983), tilt after-effect (Pizzamiglio *et al.*, 1984), light-displacement discrimination (Blythe *et al.*, 1986), spatial summation across the vertical meridian (Marzi *et al.*, 1986) and colour detection and discrimination (Stoerig, 1987) have also been described.

While some patients retain these functions without having any conscious awareness of the stimuli ('blindsight', Weiskrantz *et al.*, 1974), others report conscious percepts such as 'dark shadows' (Barbur *et al.*, 1980), 'waves' (Weiskrantz, 1986), visual 'pin

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pricks' (Richards, 1973), 'white halos' (Perenin and Jeannerod, 1978), provided that the stimuli have great physical salience and contrast. Whether these differences in awareness of the stimuli are due to the activation of different neural substrates (e.g., entirely extrastriate as against partially striate dependent mechanisms), or just to different degrees of activation (below and above visual threshold) of a common neural mechanism, is at the moment a matter for speculation. Our present study further examines the occurrence of visually-guided behaviour in the absence of stimulus awareness, which constitutes 'blindsight'.

Basically, two main methodological approaches have been developed so far to investigate this peculiar phenomenon. The first derives from animal research (Cowey, 1967; Mohler and Wurtz, 1977) and employs forced-choice responses to visual events presented within the field defect. The human subjects, like the monkeys, are faced with two alternative stimuli (or more) and must always choose between them even when the stimuli are not consciously reported.

With the second approach, which is mainly derived from psychophysical studies in normal subjects, possible influences on responses to stimuli in the intact hemifield from previous or simultaneous stimulations in the blind hemifield can be evaluated (Singer *et al.*, 1977; Marcel, 1983; Pizzamiglio *et al.*, 1984; Marzi *et al.*, 1986). This approach makes it possible to compare and to reveal interactions between the two halves of the visual field without introducing shifts in response criterion (*see* Campion *et al.*, 1983), unbalancing stimulus presentations (randomized vs blocked) and side-biasing attentional mechanisms (Tassinari *et al.*, 1987), all factors known to influence visual performance.

By stimulating both hemifields of hemianopic patients we have recently found that 4 out of 20 of these patients showed cross-midline interactions. Like normal subjects they showed spatial summation in their intact hemifield, that is, faster reaction times (RTs) to 2 simultaneous flashes than to a single flash. Unlike normal subjects, 16 hemianopes did not show summation when the 2 flashes were presented to opposite hemifields. However, 4 patients showed significant evidence of interfield summation even though they were consistently unaware of, and unresponsive to, the stimuli presented to the anopic hemifield. This evidence can be considered as a reliable indication of 'blindsight', the occurrence of which should, however, be considered infrequent on the basis of the same evidence.

In the present study we tested 4 patients with the same paradigm of spatial summation and in addition with a RT paradigm designed to study interfield interactions in the temporal domain. Evidence that visual inputs separated in time can be integrated across the midline or in the blind hemifield by hemianopics has already been provided by Singer *et al.* (1977) and Blythe *et al.* (1986). The former study showed that visual stimulation of a point in a field defect could reset the visual detection threshold of a previously adapted symmetric point in the opposite normal hemifield. The other study (Blythe *et al.*, 1986) described 2 subjects with good discrimination for the direction of apparent displacement of two lights sequentially flashed in the scotoma with an interstimulus interval of 800 ms. Normal subjects show a slowing in RT when requested to respond to the second of a pair of stimuli presented in rapid succession (Psychological Refractory Period, PRP; *see* Welford, 1952). In principle, hemianopic subjects displaying 'blindsight' could show the same effect when the 2 stimuli in sequence are presented, one to the 'blind' and the other to the normal hemifield. In the absence of conscious detection of the first stimulus, any significant slowing of the response to the second stimulus would be evidence for unconscious processing of the former stimulus, i.e., for 'blindsight'.

In the present study we compared in the same group of patients data obtained from a spatial summation task and a temporal interfield interaction task with data obtained with a more traditional approach involving forced-choice responses. Manual pointing has been repeatedly studied with forced-choice paradigms and has been reported to be preserved both in monkey and in man after occipital lobe damage (Weiskrantz *et al.*, 1974; Feinberg *et al.*, 1978). To our knowledge, all studies on human subjects have been performed with the subjects maintaining central fixation while pointing to the visual targets. However, recently it has been shown in normal subjects (Fisk and Goodale, 1985) that pointing accuracy is increased by simultaneously looking at the performing hand. We therefore decided to adopt a paradigm in which, after the stimulus was flashed within the scotoma, the patient was asked to point at 1 out of 4 possible targets while at the same time shifting his gaze in the same direction. We evaluated performance not only by using a simple regression analysis but also in a more quantitative manner by determining the probability distribution of hits for each position.

We hoped with this combination of tests to find out whether the direct and indirect methods of assessing 'blindsight' produce concordant or dissonant results. If some cases produce concordant results with different methods while others show dissonant results with the same methods, an attempt can be made to relate these discrepancies to possible differences in site and extent of their lesions.

SUBJECTS AND METHODS

We have studied 4 male patients with a homonymous field loss due to vascular infarction in the territory of the posterior cerebral artery. Informed consent on the experiments was obtained from all patients. They had no signs of paresis, aphasia, extinction of the stimulus or spatial neglect. Their mean age was 68.2 (range 65–72) yrs. The mean lesion-testing time interval was 42.5 (range 12–20) months. The patients were admitted to the study after dynamic visual field mapping performed in 2 patients (Cases 1, 2) with computerized perimetry (Perikon-Optikon) and in the other 2 cases (Cases 3, 4) with standard (Goldmann) perimetry (*see* fig. 1 for details of the methods and for results). It is important to mention that perimetric sparing near the fovea in the blind field in no case exceeded 5° on the horizontal meridian. Before formal testing began the visual field defects were also mapped with the same stimuli subsequently used in the experiment. The CT scans of the 4 patients are shown in fig. 2.

Spatial summation

The apparatus and the experimental procedures were the same as those described by Marzi *et al.* (1986). The patient sat in a partially sound-proof room in front of a perimetric bar with the head restrained by a chin and a front rest. Four light-emitting diodes (LEDs) were positioned on the bar, 2 for each visual field, at 10° and 30° from the fixation point along the horizontal meridian. A closed circuit TV system

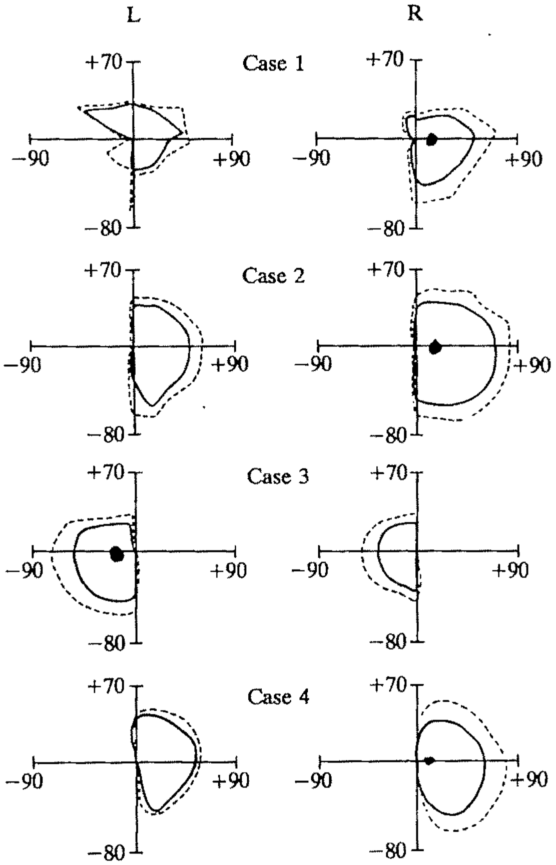

FIG. 1. Visual fields measured with standard or computerized Goldmann perimeter for each eye of the 4 patients. The detection limit for this large target (64 mm^2) is shown by the broken line and that for the small target (1 mm^2) by a continuous line. The luminance of the target was 314 cd/m^2 and that of the background was 3.14 cd/m^2. The blind spot is shown in black. L and R denote left and right eye, respectively. The apparent homonymous bilateral field loss in the lower hemifield in Case 4 is the result of a minor perimetric artefact related to the use of a standard (noncomputerized) Goldmann perimeter.

allowed the experimenter to check the subject's eye position during stimulus presentation and thus eliminate those trials in which eccentric fixation or a saccadic eye movement occurred. A brief acoustic tone, delivered binaurally via earphones, informed the subject that, after an unpredictable delay ranging from 1 to 3 s, 1 or 2 stimuli would occur in any of the previously specified positions. The subject's task was to press a key with his thumb as fast as possible following presentation of either 1 or 2 simultaneous flashes in any of the 4 spatial locations. The hand used for the response was alternated between the experimental sessions. The dependent variable was visuomotor reaction time (RT) measured with an electronic clock to the nearest ms. Each session consisted of a total of 192 flash presentations subdivided in five randomly arranged conditions. There were 48 single stimuli in the spared hemifield (S), 48 single stimuli in the anopic field, 48 double stimuli in the same hemifield—24 in the normal (D1) and 24 in the abnormal hemifield—and 48 double stimuli with 1 stimulus in each hemifield (D2). RTs faster than 150 ms (anticipations) or longer than 900 ms (misses or retardations) were rejected and replaced at the end of each session.

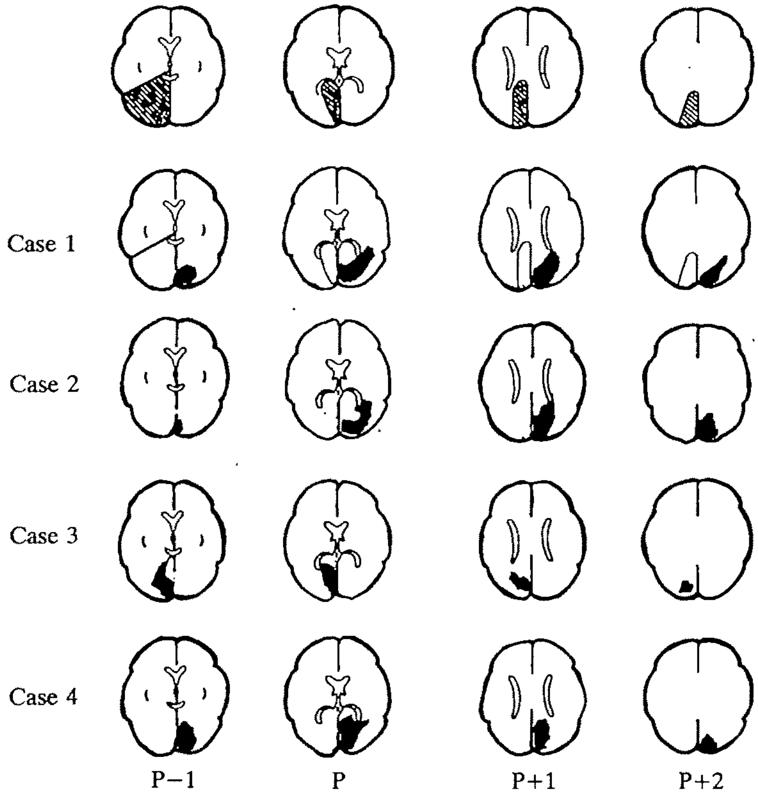

FIG. 2. Outline tracings of subjects' CT scans. Lesional areas are shown in black. The templates have been taken from McAuley and Ross Russell (1979). The upper set of templates shows the calcarine area (dotted) and the territory supplied by the posterior cerebral artery (hatched). The right side of the brain is shown on the right side of the template.

Usually, a session lasted about 30 min and each patient was tested for 5 sessions at least (range 5–9), providing no fewer than 600 RTs for statistical analysis. The luminance of each LED was about 40 cd/m^2 and that of the background was about 0.15 cd/m^2. The duration of the flash was 5 ms and its hue was greenish.

No patient was able to detect stimuli projected onto the optic disc in the normal hemifield, indicating that stray light could not explain any blindsight phenomenon in our experimental situation (*see* Campion *et al.*, 1983). Before formal testing began subjects were trained to master the task and in particular to maintain fixation and respond as quickly as possible to all stimulus presentations in every condition (S, D1 or D2). Subjects were informed on some trials that they might fail to see the flash presentations because the stimuli would be presented to the anopic area. However, they were encouraged to press the key whenever they perceived a light, even faint, in the anopic field. Stimulus presentation was controlled automatically by means of a Tektronix 4051 computer. No hemianopic subject ever responded to stimuli confined to the blind field; for statistical analysis the median RT was therefore calculated for only three conditions (S and D1 in the normal hemifield and D2 in both hemifields) and averaged across sessions and across the different eccentricities of stimulus presentations. The latter averaging was justified by the lack in normal subjects of any interaction between eccentricity and summation effect (either within or between hemifields) (G. Tassinari and others, unpublished results). Group analysis was undertaken by means of t tests, and single case and single session analysis of individual patients by a nonparametric test (median test).

Temporal interfield interactions

The general experimental arrangement was similar to that of the previous experiment. In this second task, however, the subject was faced with only 2 LEDs, one for each hemifield, mounted on the perimetric bar at 10° of eccentricity along the horizontal meridian. Eye position was checked as above.

Each session included 64 flash presentations, half as single (S) stimuli in the normal hemifield, and half as double (D) sequential stimuli across fields. In the latter condition the first stimulus was always flashed in the scotoma while the second stimulus always appeared on the spared side. Each trial began with an acoustic warning signal delivered through earphones, followed after a random interval ranging from 1 to 3 s either by 1 (S condition) or 2 (D condition) flashes in rapid succession. The subject's task was to press a key with his thumb as quickly as possible following the appearance of a flash in the spared hemifield, that is, either a single flash (S condition) or the second of 2 lights (D condition). Only the hand contralateral to the field defect was tested. Since in normal subjects PRP has classically been reported to occur for stimulus onset asynchronies (SOA) of no more than 500 ms (Welford, 1952, 1980), 4 different SOAs—100, 200, 300 and 900 ms—were chosen, 3 within the range of PRP and the last outside it. The interval between warning signal and visual stimulus was randomized so that subjects could not rely on temporal cues for responding. Single and double stimuli were alternated in a random way. RTs faster than 150 ms or longer than 900 ms were rejected and replaced at the end of each session.

Usually a session lasted about 15 min and each patient ran 4 sessions providing a total of 256 RTs for analysis, 32 for each condition and each SOA value. The luminance values for flashes and background were the same as in the first experiment but the flash duration was increased to 50 ms. Even with this stimulus duration no patient detected the stimuli projected onto the optic disc in the normal hemifield.

For statistical analysis, the median RT was calculated for each SOA in the two experimental conditions (S in the normal hemifield and D across hemifields) and averaged across sessions. Single case analysis was performed by means of paired t tests.

Manual localization task

The general apparatus was the same as in the two previous experiments. The head of the patient was restrained by a chin and a front rest and the arms were comfortably positioned on a start platform. Four LEDs were placed in the perimetric bar at 10°, 20°, 30° and 40° from the fixation point along the horizontal meridian. The luminance of targets and background were as above, the duration of flash was 100 ms, a duration still well below the latency of a saccade. As in the two previous experiments, flashes presented within the blind spot of the spared hemifield went undetected. Room luminance was such as to allow vision of the LEDs even when they were not switched on. The two visual hemifields were explored separately in different sessions according to a random sequence. Eye movement and inaccurate fixations were checked as above. While the subject was keeping his gaze on the fixation point a tone was delivered through earphones and, after a random interval ranging from 1 to 3 s, 1 of the 4 LEDs was switched on following an unpredictable sequence. After the flash went off the experimenter gave a verbal GO command, indicating that the subject should look and point at one of the targets with the hand ipsilateral to the stimulated hemifield. Every patient participated in six experimental sessions of 40 trials each. The hemianopic and the normal hemifield were studied 4 and 2 times, respectively. Every session lasted about 20 min. It is important to stress that in the above paradigm the subject, following stimulus presentation, was requested to shift his gaze from the fixation point onto the likely site of stimulation and to point at it. The subject was therefore performing in a condition where feedback from the hands and the position of the switched-off LEDs were available. In addition to the above pointing task, 2 out of the 4 patients were tested in a condition (*see below*) in which pointing at the target was performed without shifting the gaze from the fixation point. In such a condition, when the patients pointed at stimuli presented in their abnormal hemifield they worked without receiving, because of their field defect, any conscious visual feedback from their hands and/or switched-off LEDs. For comparison, accuracy in the intact field for both conditions of pointing was also checked.

We performed three separate statistical analyses on the data. First, a nonparametric analysis (χ^2, one sample) was undertaken on the total number of indications for each position in order to assess the presence of any bias towards a particular spatial location. Secondly, we compared the actual with the expected number of hits for all positions together using a binomial test. Thirdly, a linear regression analysis was performed to correlate manual response and flash position for each eccentricity.

RESULTS

Spatial summation

In this task none of the hemianopic patients responded to 1 or 2 stimuli in the abnormal hemifield, nor did they give verbal reports of visual sensations following stimuli presented in that part of the field. Confirming previous evidence (Marzi *et al.*, 1986) all 4 subjects showed a significant summation effect, that is, RT was faster for 2 lights than 1 projected to the normal hemifield (S = 391.75, D1 = 371.74, t = 3.28, df = 3, $P = 0.04$, t test, median RT average across all sessions for all subjects; *see* fig. 3A).

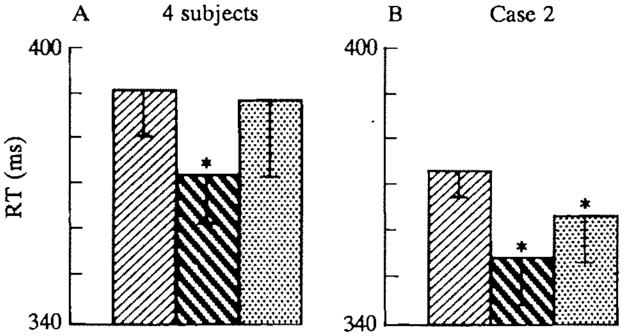

Fig. 3. Spatial summation task. A, mean RTs of the 4 patients in the three conditions of stimulus presentation. B, individual results in Case 2. SDs are indicated at the top of the histogram columns. In both A and B an asterisk denotes values significantly different from the S condition. Thin hatched bars = S; thick hatched bars = D1; dotted bars = D2.

The correspondence between these data and those obtained in normal subjects (Tassinari *et al.*, 1984, and unpublished) suggests the occurrence of a normal summation in the spared hemifield. Such a control is critical because the lack of spatial summation in the intact hemifield would have raised the possibility of a general perceptual impairment and no reliable conclusion about blindsight could have been drawn.

Two subjects (Cases 2, 3) showed a significant spatial summation across the vertical meridian in at least one testing session, even though they were never aware of visual stimuli projected in the scotoma. In Case 3, four out of five sessions went in the expected direction and in 1 case the difference between single and double contralateral stimulation was statistically significant (session 3, S = 397 ms, n = 48; D2 = 377.5 ms, n = 48; corrected $\chi^2 = 6$, $P < 0.02$, median test). In Case 2 a reliable summation effect was present in two whole sessions out of seven (session 3, S = 381 ms, n = 48; D2 = 356 ms, n = 48; corrected $\chi^2 = 7.04$, $P < 0.01$, median test; session 6, S = 370 ms, n = 48; D2 = 348 ms, n = 48; corrected $\chi^2 = 3.37$, $P < 0.05$, median test). Furthermore, after combining all RT data (n = 840) across sessions in this patient (*see* fig. 3B), we found an overall interfield summation effect (S = 373 ms (n = 336), D2 = 363 ms (n = 336), corrected $\chi^2 = 4.34$, $P < 0.05$, median test). The other 2 patients did not show any reliable difference between the S and the D2 conditions.

Temporal interfield interactions

As in the previous experiment, no patient ever reported having perceived any light in his anopic hemifield. By combining data across SOAs within the PRP range (100–300 ms) we found a significant slowing of RTs for double sequential (D) stimuli in a single subject (Case 2; *see* fig. 4) when compared with single stimuli (single = 316.2 ms, double = 336.5 ms, t = 2.24, df = 95, $P = 0.02$). No difference was found for SOAs outside the PRP range (900 ms): single = 332.2 ms, double = 320.6 ms, t = −1.12, df = 31, n.s.). The PRP-like effect was completely accounted for by differences in the first 2 intervals (100 and 200 ms) (S−100 = 305.8 ms, n = 32; D−100 = 337.8 ms, n = 32; t = 2.58, df = 31, $P = 0.01$; S−200 = 311.4 ms, n = 32; D−200 = 350.9 ms, n = 32; t = 2, df = 31, $P = 0.05$).

No significant effects related to the stimulation of the hemianopic side were found in the other 3 patients (*see* fig. 4).

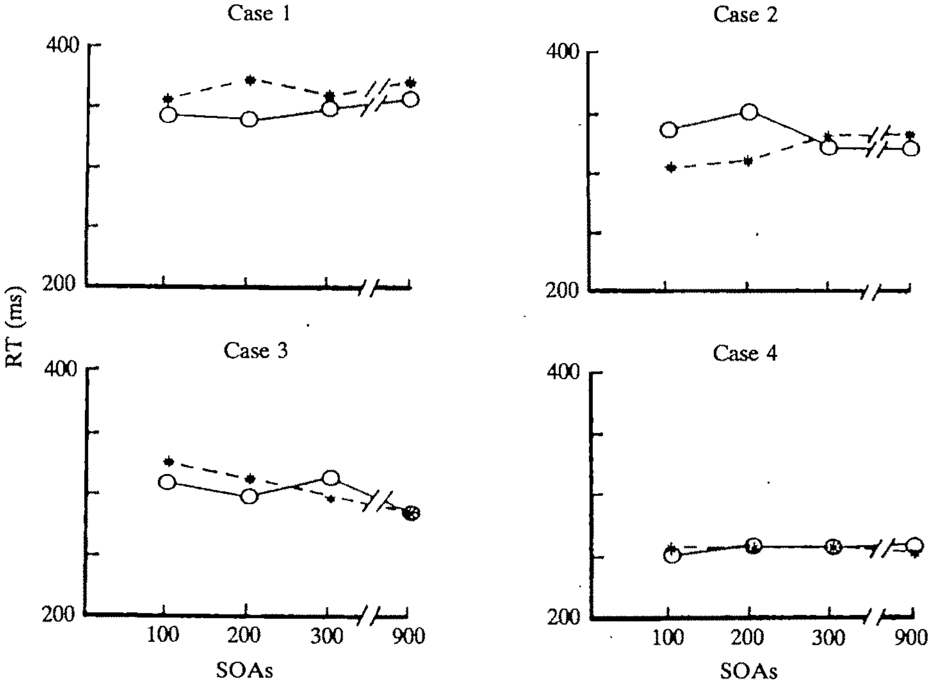

FIG. 4. Individual mean RTs of the 4 patients at various interstimulus intervals for the temporal interfield interactions task. Open circle = double, asterisk = single. SOAs = stimulus onset asynchronies.

Manual localization

All 4 patients performed the task with great accuracy in their spared hemifield. The percentage of hits for each position was 100% and the coefficient of linear correlation (r) between averaged hand indications and target positions was 1.

Confirming the results of the previous 2 experiments the performance of Case 2 in the anopic hemifield was well above chance and better than that of all the other patients (*see* fig. 5).

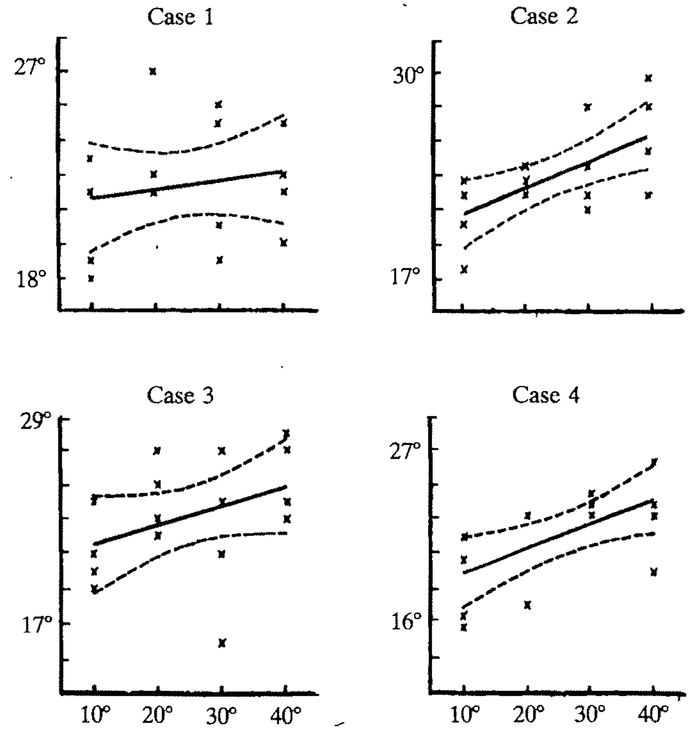

FIG. 5. Manual localization task. Performance of the 4 patients in the free-gaze pointing condition. The abscissa indicates (in deg of visual angle) the 4 positions of stimulus occurrence. The ordinate shows the response sites (in deg). The regression lines are indicated as continuous lines. The interrupted lines define 95% confidence limits. Each point indicated with the symbol 'X' represents the mean of the 10 pointing responses obtained in each session. Because of the overlapping of 2 or more values, in some graphs there are less than 4 Xs.

The regression analysis performed after averaging hand indications across the four sessions was highly significant ($r = 0.98$, $df = 3$, $P < 0.007$) and the global rate of hits/number of indications was also significant (33%, $n = 160$, expected probability of hits = 25%, observed hits = 52, $U = 2.15$, $P = 0.0069$, binomial test). At 3 out of 4 eccentricities (10°, 20° and 40°), Case 2 scored 37%, 39%, 36%, respectively, that is, well above the chance value of 25%. At 30° eccentricity he scored only 18%.

Two other patients showed some evidence of correctly locating visual targets in their blind areas. For Case 3 r was 0.87, a rather high value, although it only just approached significance (df = 3, $P = 0.06$), and the global rate of hits/number of indications was 31% (U = 1.55, $P = 0.12$). At all 4 eccentricities his scores were above chance level although not significantly (10° = 33%, 20° = 28%, 30° = 29%, 40° = 34%). Case 4 showed a significant correlation (r = 0.90, df = 3, $P = 0.04$) and a very high number of hits at 10° eccentricity (46%, n = 76, expected probability of hits = 25%, observed hits = 29, U = 2.75, $P = 0.005$, binomial test). He scored at chance in the other locations. Finally, as in the other tasks, Case 1 did not show any indication of above-chance performance following stimulation of the anopic hemifield. The unexpectedly high frequency of positive results (3 out of 4 subjects) led us to attempt a more direct comparison between the above task and the pointing task more often reported in the literature, namely, a paradigm in which the subject maintains central fixation during all stages of the task. In such a condition the subject cannot see his hand while pointing to stimuli presented in the hemianopic field, while in the former paradigm the subject can move his gaze and therefore is able to see his hand while pointing to stimuli presented to the hemianopic side. It is important that in this last condition, when stimuli were presented in the spared field, the percentage of hits (calculated as hit responses to an area of 6° around the site of real occurrence of the stimulus) approached but did not reach 100% and the coefficient of linear correlation (r) approximated to 1. This result indicates that even in the normal hemifield the two conditions of gaze differ in difficulty in that the fixed-gaze condition does not yield an errorless performance as in the free-gaze condition. Only 2 of the above 4 patients were available for this study (Cases 3, 4). Case 3 was tested in two sessions and did not show any significant correlation between site of stimulation and response. Case 4 was retested in six sessions in both pointing tasks using a schedule in which the two conditions of fixation were alternated in a random sequence. The localization performance in the condition in which the patient could freely

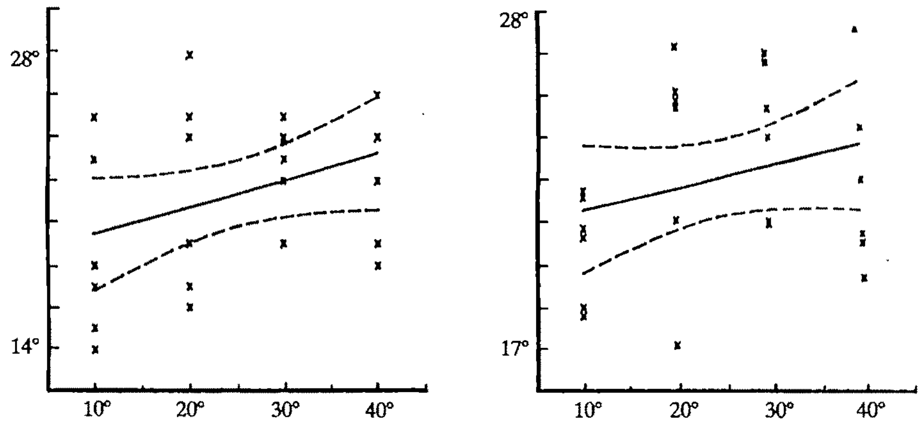

FIG. 6. Manual localization task. Performance of *Case 4* in the free-gaze pointing condition (*left side* of fig.) and in the fixed-gaze pointing condition (*right side* of fig.). In some cases, because of the overlapping of two or more values, the graphs show less than 6 Xs. *See* fig. 5 for explanations.

move his gaze while pointing was again reliable (r = 0.88, df = 3, $P = 0.05$; *see* fig. 6). On the contrary, performance in the fixed gaze condition did not yield any positive correlation between stimulus position and manual response (r = 0.56, df = 3, n.s.).

To analyse these data further we constructed a scatter plot on all averaged data for each session of the two testing conditions and performed a general regression analysis. This much more conservative analysis confirmed that Case 4 performed better when he was allowed to shift his eyes to localize the position of flash presentation (r = 0.37, df = 23, $P < 0.03$) than when he had to maintain steady fixation (r = 0.27, df = 23, $P = 0.09$).

DISCUSSION

At least three aspects of the present results require discussion. First, our results allow an intraindividual comparison of tests of blindsight under different response conditions. In the two tests of either spatial or temporal interfield interactions, the subject was not required to make guesses about a visual stimulus of which he was unaware but was simply asked to respond to a stimulus that he could normally perceive in the good field. With this paradigm the presence of unconscious visual sensitivity in the hemianopic field can be assessed indirectly by the influence exerted by the stimulation of that field on the performance in the normal field. In the third task involving spatial localization with or without continuous fixation, the subject was asked to guess as to the location of a stimulus that he could not consciously perceive. If, as proposed by Campion *et al.* (1983), blindsight can in part be considered as merely a shift from a more conservative to a laxer response criterion, the likelihood of finding blindsight should vary between the two paradigms described above. In particular, it should be more difficult to find evidence of blindsight with the former paradigm than with the latter, given that the former does not require any shift in response criterion while in the latter the patient is forced to guess as to the stimulus location, that is, to adopt a less conservative criterion. Our results from Case 2 clearly support the notion that blindsight, at least in this patient, was not dependent on the response criterion since he showed clear evidence of blindsight independently of the paradigm used. In our study, when present, dissociations in performance among tasks do not depend on the adopted criterion as is shown by Case 4 in whom we found a reliable residual capacity in the pointing task performed under free-gaze conditions but not in either the spatial or the temporal summation tasks or in the localization task under fixed-gaze conditions. The good concordance that we found in Case 2 among different indices for residual vision is in agreement with the recent study by Blythe *et al.* (1987) using various forced-choice paradigms in patients with residual conscious vision for bright and moving lights. A similar concordance among different visual abilities has been reported in a study by Perenin and Jeannerod (1978) in which residual form discrimination in 2 out of 6 hemidecorticate subjects was accompanied by good performance in visual localization, and by the conscious perception of ‘a rather bright light arising in their impaired visual field’. In contrast to the above two studies, in the present report none of the patients, and not even our best subject (Case 2) ever experienced any visual sensation within the field defect in the course of testing. Nonetheless, concordance among different indices was more common than dissociation. As to the temporal interfield interaction experiment described in the present study, to our knowledge this is the first finding of a 'phasic' inhibition on the normal hemifield by the hemianopic side, in agreement with general theories of the PRP. The results in Case 2 are indicative of a PRP shorter than that seen in normal subjects but the robustness of the effect at short SOAs and the relatively small number of trials necessary to obtain it are promising indications for using this paradigm as an effective means of assessing blindsight.

A second aspect of our study concerns the comparative effectiveness of the different paradigms for assessing the presence of blindsight. In this respect the spatial localization task appears more suitable than interfield summation for quick detection of blindsight. On the other hand, interfield summation was specifically designed to be very conservative (Marzi *et al.*, 1986) and therefore it can be used to validate the results obtained with pointing.

Finally, some comments as to the difference in successful localization between the free and the fixed-gaze pointing condition are merited. First, it should be mentioned that there is a converging indication that the type of response paradigm used, rather than the kind of stimulus, can be crucial in revealing blindsight (Weiskrantz *et al.*, 1974; P. Stoerig, 1989). Secondly, there is clear evidence that motor commands to different effectors (eye, head, hand) are delivered simultaneously in normal man during an overt orienting response to simple lights (Biguer *et al.*, 1982). Moreover, final accuracy is greatly improved by simultaneous looking at the target (Fisk and Goodale, 1985), vision of the hand (Prablanc *et al.*, 1979) and continuous inflow of kinaesthetic and/or efference copy signals from the arm movement (Goodale *et al.*, 1986). In our free-gaze pointing condition all this information is available, whereas in the fixed-gaze condition one or more aspects are lacking. This different level of difficulty is witnessed by the observation that in the normal hemifield of the same patients, accuracy of pointing is greater in the free than in the fixed-gaze condition. As far as performance in the anopic field is concerned, in the fixed-gaze condition, light localization can rely only on unconsciously acquired visual information concerning target position, working space and hand trajectories, whereas in the free-gaze condition, patients could combine unconsciously acquired information on target position with the awareness of working space and of hand trajectories during the execution of pointing. Thus the comparatively greater difficulty and the consequent deterioration in performance in the fixed-gaze paradigm can contribute to obscure the presence of blindsight. It is possible, in principle, that extensive training (*see* Zihl and Werth, 1984) might cancel the differential effectiveness of the two paradigms in revealing blindsight.

The 2 patients in the present study in whom the two paradigms have been compared showed a correlation between target and pointing only when their gaze was unrestrained while responding. Since a behaviour such a pointing to lights can actually be considered like the global nonpredictable result of several neural modular computations, a parsimonious interpretation of our findings is that a damaged neural system can better accomplish a good performance when all available resources are operating simultaneously, as in the free-gaze condition, than when they are not, as in the fixed-gaze condition. This view is analogous to that proposed in normal use, where different levels of performance can be established as a function of the number of effectors involved in the visuomotor behaviour (Jeannerod, 1986).

Until now all spatial localization tasks employed in studying blindsight have been of the fixed-gaze kind, i.e., involving conditions of maximal difficulty. We suggest that in such conditions the incidence of blindsight could be underestimated and that adopting a routine test for the quick screening of blindsight (and/or conscious residual vision) based on spatial localization in a free-gaze pointing condition would detect more patients showing blindsight and therefore would permit more quantitative studies on this intriguing phenomenon.

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COGNITIVE AND MOTOR DEFICITS IN THE ACQUISITION OF AN OBJECT RETRIEVAL/DETOUR TASK IN MPTP-TREATED MONKEYS

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SUMMARY

To assess functional changes following treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in monkeys, we studied a task that reveals sensitivity to dopamine deficits under various conditions. The task required retrieval of a banana slice from a transparent box that is open on one side and fastened to a tray. Successful performance required the subject to suppress a tendency to reach directly at the reward while (1) orientation of the open side, (2) position on the tray, and (3) position of the banana in the box were manipulated in order to vary the cognitive and motor difficulty of the trial. African green monkeys (*Cercopithecus aethiops sabaeus*) were treated with MPTP (1.5–1.6 mg/kg cumulative dose over 4–5 days). A control group was sham treated ($n = 12$). MPTP-treated subjects either became severely symptomatic, showing motor impairments that prevented them from performing, or showed no gross motor impairment ($n = 6$) in spite of major depletions in dopamine concentrations. MPTP-treated subjects showed impaired acquisition of the task when tested 8–12 months later. They made more errors during the sessions, specifically on the trials that were related to cognitive complexity, such as attempting to reach directly towards the reward through the transparent side of the box (*a barrier reach*), instead of reaching around it (*detour*) into the open side, as well as other awkward, perseverative or delayed reaches. MPTP appears to cause both cognitive and motor deficits in the acquisition of this task 8–12 months after treatment, even in the group of monkeys which never showed gross motor deficits.

INTRODUCTION

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes movement disorders and neuropathological changes that are similar to those seen in Parkinson's disease (Burns *et al.*, 1983; Langston *et al.*, 1983; Stern and Langston, 1985). In nonhuman primates, treatment with MPTP results in progressive akinesia, rigidity, flexed posture, difficulty in initiating movement, and postural and resting tremors (Chiueh *et al.*, 1985; Brooks *et al.*, 1986; Jenner and Marsden, 1986; Mitchell *et al.*, 1986*b*; Nomoto *et al.*, 1986; Clarke *et al.*, 1987). Reductions in the level of the neurotransmitter dopamine (DA) and its metabolites are observed in the substantia nigra (Kitt *et al.*, 1986; Mitchell *et al.*, 1986*b*; Nomoto *et al.*, 1986; Elsworth *et al.*, 1987*b*) and in the caudate and putamen

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(Mitchell *et al.*, 1986*a, b*; Elsworth *et al.*, 1987*a*), as well as other neurochemical changes that are also characteristic of Parkinson's disease (Forno *et al.*, 1986; Mitchell *et al.*, 1986*b*). The MPTP model in the primate has thus been suggested to mimic both the pathophysiological and behavioural sequelae of human idiopathic Parkinson's disease.

Most studies of MPTP in primates have relied on observational or activity analyses (Chiueh *et al.*, 1984, 1985; Langston *et al.*, 1984; Burns *et al.*, 1985; Bankiewicz *et al.*, 1986; Degryse and Colpaert, 1986; Jenner and Marsden, 1986; Kitt *et al.*, 1986; Nomoto *et al.*, 1986; Mitchell *et al.*, 1986*b*), but no studies to date have examined whether MPTP induces a cognitive impairment in addition to characteristic parkinsonian motor abnormalities in monkeys. Few studies have investigated potential motor capabilities using tests that are challenging or are comparable to the tracking or tracing tasks used in the neurological examinations of parkinsonian patients (Bowen *et al.*, 1972). The use of nonhuman primates makes it possible to study cognitive abilities as well as motor control or coordination following MPTP treatment. The neurochemical and neuropathological changes following MPTP toxicity can then be correlated with any functional deficits which might be detected. Neuropsychological and cognitive changes can also be compared with those in Parkinson's disease and after MPTP toxicity in human patients. These studies, therefore, might help to establish the extent to which MPTP-induced neurochemical lesions model Parkinson's disease and to improve the understanding of the neuropathology of that disorder.

It might be predicted that MPTP treatment would produce cognitive impairments, particularly on tasks that are sensitive to the functional integrity of the frontal lobes (Johnson *et al.*, 1968), and one study in patients has reported cognitive or 'intellectual' deficits following accidental MPTP intake (Stern and Langston, 1985). Nondemented patients with Parkinson's disease also have neuropsychological deficits even in the early stages of the disease (Lees and Smith, 1983) although their intellectual function, measured by New Adult Reading IQ tests and recognition memory tests (Warburton, 1967; Reitan and Boll, 1971; Loranger *et al.*, 1972; Lees and Smith, 1983), is generally normal. However, they have significant difficulty on 'executive' tasks, such as performing mental computations that require shifting conceptual sets (Talland and Schwab, 1964; Bowen *et al.*, 1975; Lees and Smith, 1983), planning (Stern *et al.*, 1983; Taylor *et al.*, 1986; Benecke *et al.*, 1987), and learning-memory processes (Weingartner *et al.*, 1984), and they often make 'perseverative' or repetitively incorrect responses (Bowen *et al.*, 1975; Lees and Smith, 1983). Selective impairments on these tests are also known to result from frontal lobe dysfunction (Milner, 1963; Luria, 1965). These impairments are similar to the cognitive deficits reported in patients exposed accidentally to MPTP (Stern and Langston, 1985). In nonhuman primates, lesions of the frontocaudate circuits, caused by damage either to the prefrontal cortex or to the caudate nucleus produce analogous behavioural impairments (Iversen and Mishkin, 1970). Damage to the anterodorsal head of the caudate nucleus has been associated with impairments in performing cognitive tasks. This site receives a massive neuronal projection from the prefrontal cortex and lateral convexity (Iversen and Mishkin, 1970) and both the caudate nucleus and the prefrontal cortex are important projection areas for midbrain dopaminergic (DA) systems.

It might be predicted on the basis of the literature on primates that MPTP treatment would also produce cognitive impairments, particularly on tasks that are sensitive to the functional integrity of the frontal lobes (Johnson *et al.*, 1968).

Studies of the effects of MPTP on motor behaviour in monkeys have provided some limited support for similarities to Parkinson's disease, but only scant evidence of more complex motor or cognitive difficulties. Akinesia, rigidity, postural and resting tremors, and difficulty in initiating movement have been observed (Schultz *et al.*, 1985). Quantitative assessment of hypokinesia has revealed increased reaction times, delayed onset of muscle activity, and prolonged movement times in a forearm reaching task (Doudet *et al.*, 1985). Mechanographic and electromyographic studies during the execution of simple arm movements have also confirmed disturbances similar to those reported in Parkinson's disease (Doudet *et al.*, 1985, 1986). These simpler tasks, unfortunately, might not detect more subtle deficits, such as the inability to plan and execute sequential movements which have been described in parkinsonian patients (Benecke *et al.*, 1987). Complex combinations of two or more movements are more difficult for parkinsonians than simple one-joint movements in which each movement is performed separately (Benecke *et al.*, 1987). Furthermore, the tasks studied in primates so far may not be sensitive to possible cognitive or perceptual motor dysfunction and skilled voluntary movement impairments (e.g., Tatton *et al.*, 1984).

The natural course and onset of these more subtle difficulties is not known, and studies have been carried out exclusively on patients after they have been diagnosed as having the disease or after significant MPTP effects. It may therefore also be of interest to determine whether cognitive or perceptual difficulties can be detected in the absence of more obvious motor problems.

The present study investigated the ability of monkeys to *learn* an object retrieval task that involved reaching around a transparent barrier (i.e., making a detour) in order to retrieve a reward. The acquisition, or learning, of the task by the subjects was examined 8 – 12 months after they had been treated with MPTP. The focus of the study was on monkeys that appeared to show no gross motor impairments after MPTP. Subjects which showed marked motor deficits either would not perform or were unable to move, and thus generally could not be examined without the interference of gross motor difficulties which would prevent test responses. The task not only examined various aspects of motor control but also tested planning, the association of visual information in space, the recognition of object permanence, and other features that are known to reflect mental computations or cognition (*see* Piaget, 1954; Diamond, 1989*a, b*). The subjects' acquisition of the task many months after being treated with MPTP allowed us to examine whether they were completely normal and were comparable to nontreated subjects on measures of cognitive as well as fine motor competence.

Detour ability is an important component of problem solving and skilled action, since it involves altering spatial relationships between the self and objects through movement (Piaget, 1954). With transparent barrier tasks, the visual information obtained about the presence of the reward directly in front of the subject conflicts with tactile information indicating a barrier. The development of detour ability has been studied in human infants

(Lockman, 1984; Diamond, 1989*a*) and in nonhuman primates (Moll and Kuypers, 1977; Diamond, 1989*b*). Adult rhesus monkeys with lesions of the dorsolateral prefrontal cortex perform similarly to human infants who have not developed the necessary cognitive skills (Diamond and Goldman-Rakic, 1985; Diamond, 1989*a*, *b*); they reach along their line of sight instead of making a detour reach and are not able to inhibit this response. The detour task that we adapted, therefore, has proven sensitive to frontal deficits, measures perseverative responses, and requires complex sequential motor planning. It also measures response biases such as hand preferences and provides a means to separate more purely motor difficulties from cognitive ones.

METHODS

Subjects

Subjects were adult male African green monkeys (*Cercopithecus aethiops sabaeus*) from the West Indies island of St Kitts (St Christopher-Nevis). They were housed individually in standard primate cages in natural daylight. Access to food was unrestricted; approximately 15 jumbo high-protein biscuits (Purina) were placed in a food container each morning, sufficient to ensure that a surplus was always available. Water was continuously available. Care and treatment of these monkeys were in compliance with the USPHS *Guide for the Care and Use of Animals*, and the protocols were approved by the relevant institutional review committees.

Apparatus

Apparatus used for the object retrieval testing was a specially designed Wisconsin General Test Apparatus (WGTA) that could be fastened onto the front of the subject's home cage during the test sessions. Use of the home cage environment ensured minimal disturbance to the subjects. The test apparatus consisted of a piece of hardboard (35×25 in) fixed to a wood frame. Near the centre was a rectangular opening (15×12 in) containing wire mesh with large rectangular (each 2×4 in) openings through which the subject could reach. A transparent ¼ in acrylic screen (18×13 in) covered the central opening; this functioned as a door that could be raised and lowered by means of a pulley. On the outside, beneath the central opening, were brackets that secured a tray (24×6 in). The tray contained a central groove through which the test box could be screwed onto the tray in various positions. The tray was positioned so that all regions were within reach of the subject when the screen was raised.

The test box (3×3×1.5 in inner dimension) was made of transparent acrylic (0.25 in thick) and was open on only one side. The WGTA was mounted on the front of the subject's cage so that the central opening was directly over the guillotine door of the cage. During testing the guillotine door was kept permanently up and the screen was raised on each trial so that the subject could reach through the apparatus bars onto the tray and into the test box. The experimenter sat directly across from the apparatus in order to identify and score each response made by the subject during testing.

Drug treatment

The subjects were treated i.m. with 5 or 4 repeated doses (0.3 or 0.4 mg/kg/dose over 5 days) of MPTP hydrochloride (Aldrich, Milwaukee, WI). The cumulative doses were 1.5−1.6 mg/kg for the 6 MPTP-treated subjects that are the principal focus of this report. Two of these subjects were treated 12 months before object retrieval testing and the other 4 were treated 8 months before testing. Control subjects were sham treated with saline (n = 12). Eight severely symptomatic subjects treated at the same time and on the same schedules could not be tested on the task due to severe motor impairments; therefore this report focuses on the 6 MPTP-treated subjects which did not develop gross motor deficits (termed 'asymptomatic') compared with 12 saline-treated controls.

Biochemical assessment

Assays of cerebrospinal fluid (CSF) homovanillic acid (HVA) levels, using gas chromatography-mass spectrometry (GCMS), were made in 4 of the 6 subjects before treatment with MPTP, 1 month and 12 months after treatment (Bacopoulos *et al.*, 1979). CSF was taken by cisternal puncture under ketamine anaesthesia, mixed with deuterium-labelled HVA (internal standard) and frozen in liquid nitrogen.

Behavioural procedures

Acquisition testing for this task consisted of one preliminary training session and four test sessions. The experimenter was blind to the treatment history of each subject. A subject's responses were recorded by the experimenter during the session. Responses were later entered into a computer.

First, each subject received one 10-min training session to habituate it to the WGTA and the experimenter. The banana reward (0.5 in thick slice of banana) was placed on the tray outside the subject's cage and the screen was raised. This was repeated until the subject could reach and retrieve the reward easily. Next, the test box was placed on the tray, with the open side facing the subject, and the banana slice was placed on top of or in front of the box. This was repeated several times as the monkey gradually learned to retrieve the banana by reaching directly in its line of sight.

During the test sessions the box was fastened to the tray on the WGTA outside the cage. Three variables were manipulated in order to establish the cognitive and motor difficulty associated with each trial (*see* Diamond, 1989*a*). First, the orientation of the open side of the box could be such that the open side of the box faced to the front, left, or right, relative to the subject. Secondly, the position of the box on the tray could be middle, far left, or far right. Finally, the position of the reward in the box was varied so that it was sticking partly out, or near the edge, or in the corner, or in the middle, or deep inside the box. The reward was always visible, but the experimental manipulations determined whether the reward was seen through the open or the transparent barrier side of the box.

There were four test forms that determined the configuration of these three variables. Each test form contained a number of drawings that depicted the orientation and position of the box and position of the reward on each trial. The form for the first session contained 11 trials. For all trials the box was in the middle of the tray. On the 2 trials where the opening faced to the side, the reward was sticking partly out so that a direct reach could result in retrieval of the reward. The following 3 test sessions each consisted of 20 trials. The test forms for these 3 sessions were different from each other, the second being a mirror image of the first. For acquisition testing each form was used once only. Testing was undertaken every third day.

Before the start of the test sessions the experimenter set up the WGTA and sat directly in front of the subject, with the appropriate form and sheet for scoring the responses on each of the trials. During each trial the experimenter set the box on the tray in the appropriate position for that trial. The box was screwed in place so that it could not be moved by the monkey. The experimenter signalled the beginning of a trial by showing the monkey a slice of banana and then placing it in the appropriate area inside the test box. The screen was then gently raised and the subject was required to reach and retrieve the reward from the box. The subject was allowed to try to retrieve the banana reward as long as it continued to try to act on the box in some way. The subject's movement and responses involving the tray or box were not in any way restrained.

If the subject stopped trying, the experimenter could tap on the box in order to encourage the subject to respond. If it failed to make a response for more than 20 s, the screen was lowered and the trial was repeated. If the subject continued not to respond the trial was terminated. After about 15 s (or after the subject finished eating the banana slice) the box was then set up for the next trial depicted on the test form.

Behavioural measures

During each trial the experimenter scored several responses on the trial. For every reach the subject made, three items were noted on the score sheet, outlined and defined as follows: (1) *Reach act*—reaching at the front, left, or right side of the box; (2) *Hand used*—left or right; (3) *Result*—success or failure.

A *reach act* was defined as the subject extending or moving its arm and touching the side or top of the box, the banana reward, or the inside of the box. Since theoretically the number of reaches the subject could make was unlimited (as long as the subject was attempting to retrieve the reward) this required some scoring practice on the part of the experimenter. The hand that the subject used on each response was noted as well as whether the reward was obtained on each response during the trial. Examples of some of the test trials are shown in fig. 1.

With the above information several additional variables could be derived for analyses. For example, a cognitive error occurred if the monkey reached to the closed transparent side of the box. By knowing the trial number (which determines the location and opening of the box) and the reach act (front, left, or right side) we can determine if the subject reached to the closed side of the box, instead of reaching around in order to successfully retrieve the reward. This response was termed a *barrier reach*. If the subject reached into the correct (open) side of the box but failed to retrieve the reward on that reach, this was usually due to an inability to grasp, or make the appropriate coordinated arm movements, or because the subject inadvertently pushed the banana slice further into the box. A failure to retrieve the reward when the subject made the correct reach response (through the opening) was scored as a *motor problem*. Other difficulties in responding could be indicated by the total number of reaches the subject made for each trial (*reach number*).

Although a subject might make several reaches before responding correctly on a trial, generally its competence on the task was indicated by retrieval of the reward on the first reach on any trial. If the subject retrieved the reward on the first reach on the trial, this was termed a *success*. If the subject made one or more reaches but eventually retrieved the reward, the trial was termed *correct*.

Hand preference (or *handedness*) was determined by which hand was used on the first reach of the trial, and *hand bias* was determined by the total number of left or right-hand reaches on each trial. *Awkward reaches* (Diamond, 1989*a*) occurred when the subject used the hand furthest from the open side of the box. On a new trial, the frequency of repeating the last reach act made during the previous trial was also examined. If the subject's first reach was towards the left side of the box and this was not the open side (therefore an incorrect response) and the last response on the previous trial has also been a reach towards the left side of the box, then this was considered a *perseverative response* or error. After the screen was raised, the experimenter started a stopwatch and stopped it as soon as the subject touched the box or the banana slice. This latency to respond (in s) was defined as the response *initiation time*.

Most of the responses examined in each test session were further categorized by the degree of motor or cognitive difficulty (*see* fig. 1). Prior to the analyses, the motor difficulty of each trial was rated on a scale of 1–12. If the opening was facing the monkey and the box was in the middle of the tray and the reward partly protruded, that trial was given a *difficulty score* of 1. On the trials with the lowest difficulty scores (1 and 2), the subject was only required to reach in a straight line directly in front of its body, grasp the reward, and withdraw its arm in order to retrieve the reward, rather like the movements involved in pulling a lever. As more complex movements were required, and more interference was expected from having to detour around a stationary object, the difficulty scores were increased. The highest difficulty was scored if the opening faced away from the subject, the box was on the far left or right of the tray, and the reward was deep in the front corner (score of 12). This type of trial required subtle motor control of the upper arm, forearm, hand, and digits.

Similarly, the level of cognitive ability required to solve the task and to retrieve the reward was classified a priori as *easy* in 6 and *hard* in 16 of the 60 trials included on the test forms 2, 3 and 4 based on predicted cognitive complexity. This rating was determined by the particular orientation of the box and the previous configuration of several preceding trials. For example, if there were 3 trials in which the open side of the box was facing to the left and the box was located on the far left of the tray, and then on the next trial the open side of the box was facing to the right and the box was on the far right of the tray, then this last trial was considered a hard trial. If the orientation of the box was not changed from the previous trial and the opening was facing to the front, then this trial would be considered easy. Some hard trials had low motor difficulty scores and vice versa. The trials not classed as cognitively easy or hard (38 trials) were not included in this particular analysis.

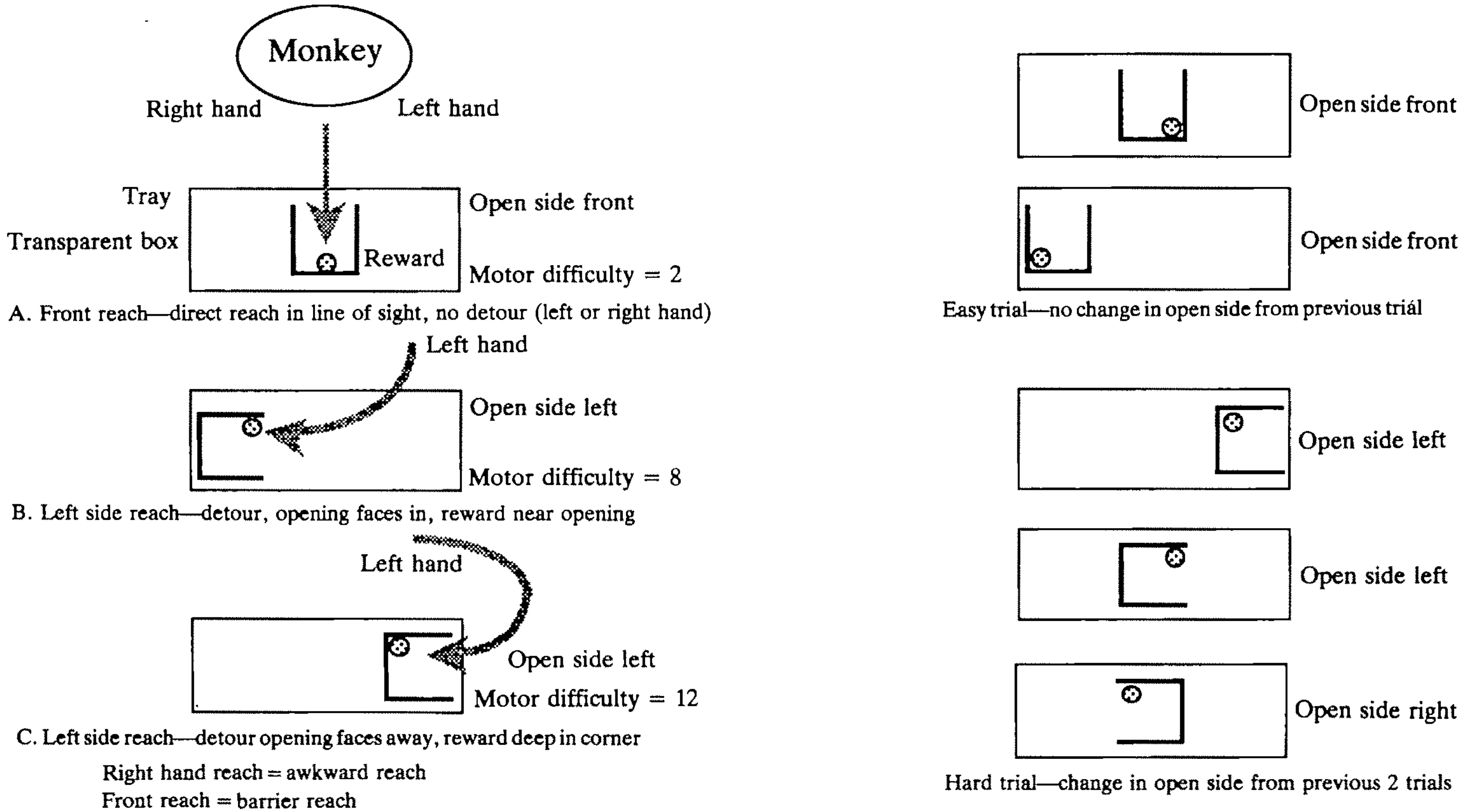
Monkey
Right hand
Left hand
Tray
Transparent box
Reward
Open side front
Motor difficulty = 2
A. Front reach—direct reach in line of sight, no detour (left or right hand)
Left hand
Open side left
Motor difficulty = 8
B. Left side reach—detour, opening faces in, reward near opening
Left hand
Open side left
Motor difficulty = 12
C. Left side reach—detour opening faces away, reward deep in corner
Right hand reach = awkward reach
Front reach = barrier reach
Open side front
Open side front
Easy trial—no change in open side from previous trial
Open side left
Open side left
Open side right
Hard trial—change in open side from previous 2 trials

FIG. 1. Diagram showing the position of the box on the tray, reward in the box and open side of the box on various types of trials. *Left*: examples of three different types of trials. In A, the subject can see the reward by looking directly into the box and reaching in its line of sight with either hand to retrieve the reward; in B, the subject can see the reward through the transparent side (front) of the box, or by looking through the open left side of the box, and can retrieve the reward by making a detour reach with its left hand; and in C, a similar reach must be made, except that the reward is deep in the front corner of the box and the open side faces away from the centre of the tray. Motor difficulty scores for the examples are shown. *Right*: examples of trials classified by cognitive level as easy or hard. For the easy trial, the open side of the preceding trial is also the front, on the hard trial, the open side faces the subject's left on the 2 preceding trials and then is switched to the right side. On this hard trial the motor difficulty score is a low rating of 4.

Statistical analyses

Statistical evaluations were made using analyses of variance (Winer, 1971). Preliminary tests of variance homogeneity, normality, and distributions satisfied the assumptions required for a standard parametric analysis of variance, with one exception. Data expressed as percentiles (which have a binomial distribution) were arc sin transformed as recommended by Winer (1971). Analysis of variance was used to determine significant effects, using the following model: main effects of Group (MPTP-treated subjects or control subjects), Session (test day, 1, 2, 3, 4), and interactions between Group and Session for each of the measures were examined. Significant interactions were broken down and reanalysed by simple main effects. Duncan's Multiple Range test, with appropriate Mean Square Error terms, was done as a post hoc test to determine the significance of individual or group differences. Analyses of the data by motor difficulty score and cognitive classification were determined similarly using a model that included the following: Group (MPTP-treated or control subjects), Motor difficulty (1 – 12), and interactions between Group and Motor difficulty, Group (MPTP-treated or control subjects), Cognitive classification (easy, hard), and interactions between Group and Cognitive classification. Significant interactions were examined as above. CSF HVA was examined similarly using a single factor analysis with a repeated measure (baseline, 1 month, or 12 months after MPTP).

RESULTS

Biochemical analyses

Baseline levels of the DA metabolite HVA were determined from CSF drawn before MPTP treatment. A one factor analysis of variance, with repeated measures, showed a significant difference in the MPTP-treated monkeys over time ($F = 33.16$, df 2,9, $P < 0.01$). One month after MPTP treatment (fig. 2) HVA CSF levels were decreased

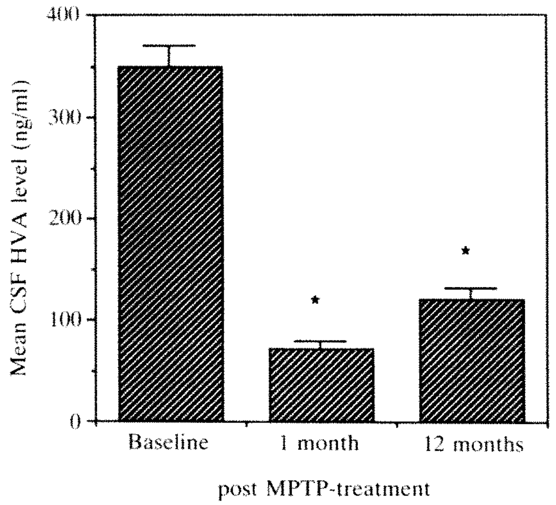

FIG. 2. Mean concentration of homovanillic acid (HVA) in CSF obtained by cisternal puncture in MPTP-treated subjects ($n = 4$). MPTP significantly reduced CSF HVA 1 and 12 months after treatment compared with baseline ($P < 0.01$*).

significantly to 20% of the baseline (from approximately 350 to 77 ng/ml). Twelve months post MPTP treatment (after the behavioural testing for this study was completed), HVA levels were still significantly decreased to 35% of baseline. Although in MPTP-treated subjects at this time point the mean concentration of CSF HVA was slightly higher, it was not statistically different from the levels determined at 1 month. Baseline levels of HVA were within the normal range determined from large numbers of samples in other subjects as determined by our laboratories (Elsworth *et al.*, 1987*a*).

Behavioural analyses

Treatment with MPTP produced obvious motor, behavioural and autonomic abnormalities in 8 subjects within a week after treatment. These subjects became severely impaired and required nasogastric feeding and special care. When tested, they were incapable of any responses on the object retrieval detour task. Quantitative assessment of their behavioural status, using observational-rating methods will be reported elsewhere. In the group of 6 subjects which are the focus of this report, no gross motor symptoms were observed by observational methods (D. E. Redmond Jr, J. R. Taylor, J. R. Sladek and R. H. Roth, unpublished data), either soon after treatment or at the time of testing, 8 – 12 months later. These MPTP-treated subjects, however, were found to have motor and cognitive impairments on the object retrieval task. These results are described in the following three sections: (1) acquisition of the task—correct and successful responses; (2) motor deficits—motor problems, reach number and initiation times; and (3) cognitive deficits—barrier reaches, perseverative responses and awkward reaches.

Acquisition. Learning, or acquisition, of the task, measured by the number of correct and successful responses, was retarded in MPTP-treated subjects (fig. 3). These subjects

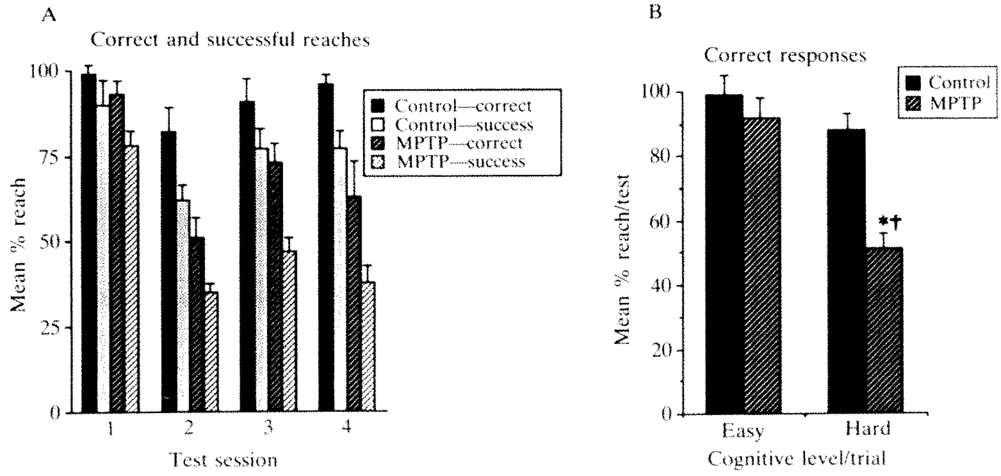

FIG. 3. *Correct* and *successful* reaches during acquisition (A) and correct responses shown as cognitive level (B) in MPTP-treated and control subjects. A, correct and successful reaches on day 1, 2, 3, 4. There were significant effects of group for both *correct* and *success*, MPTP-treated subjects making fewer correct and successful reaches on session 1, 2, 3 and 4. B, correct responses examined as a function of cognitive level. Significant differences ($P < 0.01^*$) were only observed between the groups on the hard trials and MPTP-treated subjects made significantly fewer correct responses on the hard compared with easy trials ($P < 0.01\dagger$).

made significantly fewer correct responses on the task than controls (Group F = 55.25, df 1,16, $P < 0.01$) and were less successful in obtaining the reward on the first reach (Group F = 66.43, df 1,16, $P < 0.01$) during testing. There were also significant main effects of session (correct F = 10.38, df 3,48, $P < 0.01$ and success F = 20.47, df 3,48, $P < 0.01$). On the first test day, in which the opening in the box faces most often the subject, both groups obtained the reward on 90% of the trials (*correct*) and were successful on the first reach on more than 75% of trials (*success*). On the second, third and fourth test sessions, the positioning of the reward and box are designed to be more difficult, to induce cognitive and motor challenges to the subject. The mean correct and successful responses were significantly reduced on the second session and were still different from the first on the third and fourth sessions.

Performance was in accord with the motor difficulty scale of 1 – 12, with the exception of trials with a difficulty score of 6 which seemed more difficult than predicted. On trials rated with a motor difficulty score of 6 the position of the open side of the box and placement of the reward within the box were the same configuration as on trials with a score of 12 (open side to the left or right with reward in the front corner), but with the box in the central position on the tray. For the analyses of both correct and success, respectively, there were significant effects of Group (F = 186.34 and F = 181.38, df 1,16, $P < 0.01$), Difficulty (F = 28.76 and F = 62.02, df 3,48, $P < 0.01$), and interaction between Group and Difficulty (F = 10.45 and F = 4.96, df 3,48, $P < 0.01$). As the motor difficulty increased MPTP-treated subjects made fewer correct and successful responses than did controls. For all trials, except those with a difficulty score of 6 or 12, control subjects were more than 90% correct, and on trials with a score of 1, 2, 3, 4, 5, 7 and 8 control subjects retrieved the reward on the first reach on 75% of trials. MPTP-treated subjects were > 90% correct on trials with a difficulty score of 1 and 7. Moreover, MPTP-treated subjects were only 75% successful on trials with a motor difficulty score of 1 and 2, where the opening of the box faced the subject, and 7. The percentage of correct and successful responses generally declined with increasing motor difficulty score in subjects treated with MPTP. At the highest score, MPTP-treated subjects were only 25% correct; however, controls were more than 80% correct for all trials regardless of the difficulty. Both controls made the least number of successful reaches on trials with a score of 6 and 12, controls averaged about 45%, whereas MPTP-treated subjects averaged 6%. MPTP-treated subjects made significantly fewer correct responses than control subjects on trials with a motor difficulty score of 5, 6 and 12 and were less successful on trials with a score of 5, 6, 9, 11 and 12.

When the mean number of correct responses made by the groups was examined in terms of whether the trial was classified as easy or hard, determined by the cognitive requirements, there was a significant interaction between Group × Easy/Hard (F = 13.53, df 3,48, $P < 0.01$). On the easy trials both groups were more than 90% *correct*, whereas on the hard trials MPTP-treated subjects were *correct* on 50% of the trials compared with 87% correct responses by the controls (*see* fig. 3). Examination of the interaction confirmed that while there was no difference between the groups for correct responses on the easy trials there was on the hard trials. In addition, MPTP-treated subjects were significantly worse on the hard trials than on the easy trials. MPTP-treated subjects were also not as successful at retrieving the reward on the first reach (Group F = 19.92, df 1,16, $P < 0.01$), and both controls of subjects were more successful on easy trials than on hard trials (Easy/Hard F = 65.80, df 3,48, $P < 0.01$).

Motor deficits. MPTP-treated subjects generally had more motor problems, as measured by reaching into the open side of the box but failing to retrieve the reward on the first reach (Group F = 5.21, df 1,16, $P < 0.05$ and Group×Session F = 4.18, df 3,48, $P < 0.01$). They were also significantly different from controls on the fourth session (fig. 4). They also made more reaches per trial than controls (Group×Session F = 9.29, df 3,48, $P < 0.01$), shown in fig. 5. Subjects retrieved the reward on the first reach on the first session when the opening in the box faced the subjects; however, MPTP-treated subjects made significantly more reaches than controls on the third and fourth sessions. Control subjects only made more reaches on session 2 compared with the other sessions, whereas MPTP-treated subjects made more reaches with each subsequent session.

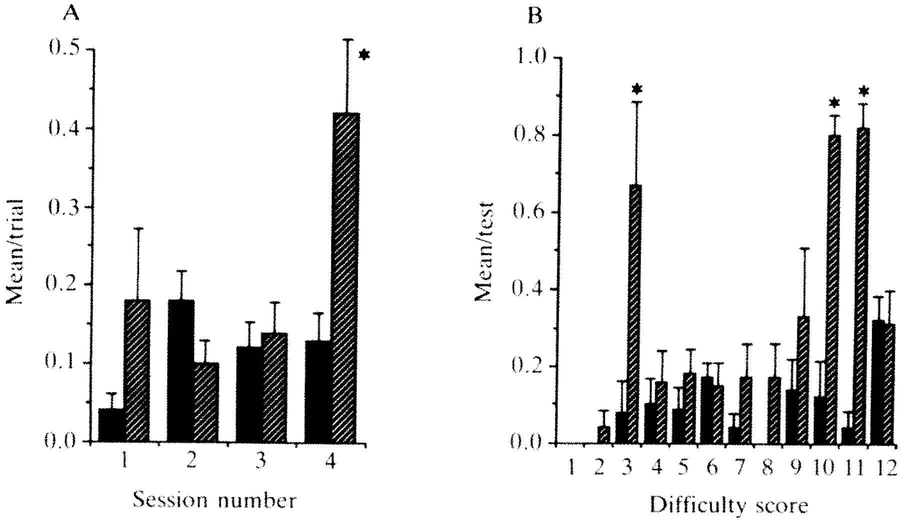

FIG. 4. Motor problems during acquisition (A), also shown by difficulty scores (B). A, motor problems during acquisition. There were significant differences ($P < 0.01$*) between the groups on session 4. B, motor problems shown with the trials classified by difficulty score. There were significant differences ($P < 0.01$*) between the groups on trials with scores of 3, 10, 11. Filled bars = control; hatched bars = MPTP-treated subject.

There were low levels of motor problems associated with trials of low motor difficulty score for both groups, except for those with a score of 3 for MPTP subjects (fig. 4). On trials where the opening of the box was facing the subject (difficulty score of 1 and 2) neither control had many motor problems and both averaged 1.0 reach per trial. For trials with a higher difficulty score MPTP subjects had more motor problems than controls. This was confirmed by a significant interaction between Group and Difficulty

(F = 2.23, df 3,48, $P < 0.01$). MPTP-treated subjects had significantly more motor problems on trials 3, 10 and 11 than controls and, unlike controls, they had significantly more motor problems on trials associated with higher difficulty scores. In addition, subjects increased the mean number of reaches with different motor difficulty scores (Group×Difficulty F = 4.65, df 3,48, $P < 0.01$), shown in fig. 5. MPTP-treated subjects were significantly increased compared with controls on trials with a score of 6, 9, 10, 11 and 12. All subjects had more motor problems on the hard trials than on the easy trials (Easy/Hard F = 7.39, df 3,48, $P < 0.01$) and they generally made more than twice as many reaches on the hard than easy trials (Easy/Hard F = 28.17, df 3,48, $P < 0.01$). MPTP-treated subjects also made more reaches than controls (Group F = 10.64, df 1,16, $P < 0.01$).

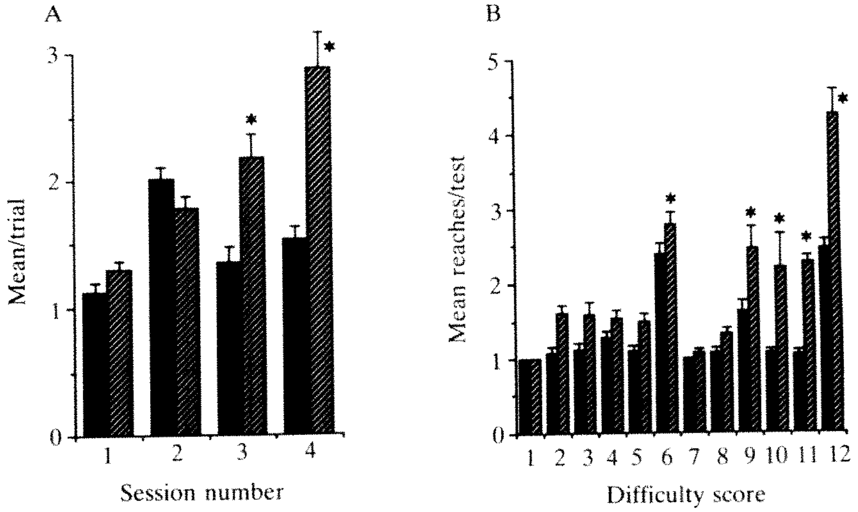

FIG. 5. Number of reaches on trials during acquisition (A) and shown as different difficulty scores (B). A, reach number during acquisition. There were significant differences ($P < 0.01$*) between the groups on session 3 and 4. B, the number of reaches shown as the trials classified by difficulty score. There were significant differences ($P < 0.01$*) between the groups on trials with a difficulty score of 6, 9, 10, 11 and 12. Symbols as in fig. 4.

On the first test session both controls averaged response initiation latencies of approximately 5 s (fig. 5). These latencies increased during the subsequent sessions. There was a significant interaction between Group and Session (F = 13.20, df 3,48, $P < 0.01$). On the final test session, MPTP-treated subjects were significantly increased (50 s) compared with controls (10 s).

There were differences between the groups in their initiation latency for trials classified by motor difficulty (fig. 6); Group×Difficulty interaction (F = 14.07, df 3,48, $P < 0.01$). MPTP-treated subjects were significantly slower to initiate reaching than controls on trials with a difficulty score of 2, 5, 6, 9, 10, 11. There was a significant interaction between the cognitive classification of the trials and whether the subjects were

MPTP-treated or controls (Group×Easy/Hard F = 6.83, df 3,48, $P < 0.01$). Subjects were slower to initiate reaching on the hard trials and MPTP-treated subjects were significantly slower than controls on both the easy and hard trials (fig. 6).

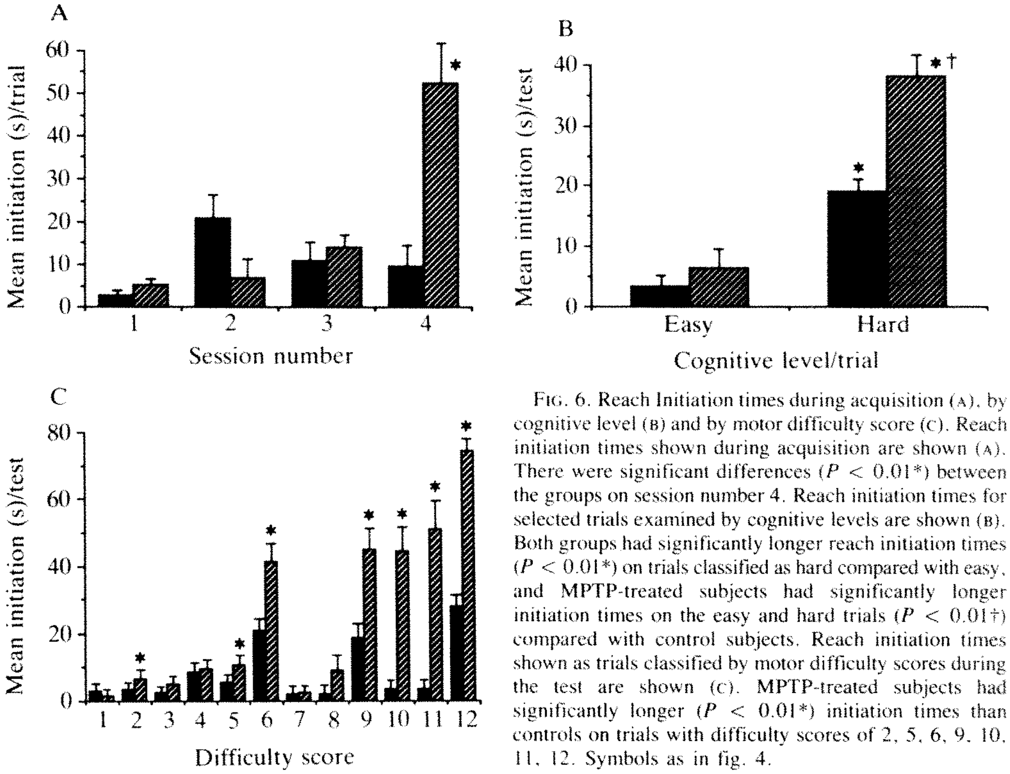

FIG. 6. Reach Initiation times during acquisition (A), by cognitive level (B) and by motor difficulty score (C). Reach initiation times shown during acquisition are shown (A). There were significant differences ($P < 0.01$*) between the groups on session number 4. Reach initiation times for selected trials examined by cognitive levels are shown (B). Both groups had significantly longer reach initiation times ($P < 0.01$*) on trials classified as hard compared with easy, and MPTP-treated subjects had significantly longer initiation times on the easy and hard trials ($P < 0.01$†) compared with control subjects. Reach initiation times shown as trials classified by motor difficulty scores during the test are shown (C). MPTP-treated subjects had significantly longer ($P < 0.01$*) initiation times than controls on trials with difficulty scores of 2, 5, 6, 9, 10, 11, 12. Symbols as in fig. 4.

Cognitive deficits. The number of reaches at the barrier was elevated in MPTP-treated subjects (fig. 7). There was significant interaction between Group and Session (F = 5.20, df 3,48, $P < 0.01$). On the first session when the open side of the box faced the subject on most trials, there were very few barrier reaches for either group. From the second session onwards, when a reaching detour around the transparent barrier was necessary to retrieve the reward on almost all trials, MPTP-treated subjects significantly increased barrier reaches. Control subjects only increased barrier reaching on the second session compared with the first. Subjects treated with MPTP significantly differed from controls on the third and fourth test sessions, making four times as many barrier reaches.

There were increases in barrier reaches in MPTP-treated subjects on trials with a difficulty score of 5, 6, 9, 11 and 12 (Group×Difficulty interaction effect F = 4.91, df 3,48, $P < 0.01$). The increased number of barrier reaches made by the MPTP-treated subjects was generally confined to the trials that were classified as being hard in terms of cognitive level (fig. 7). The interaction of Group with Easy/Hard was significant

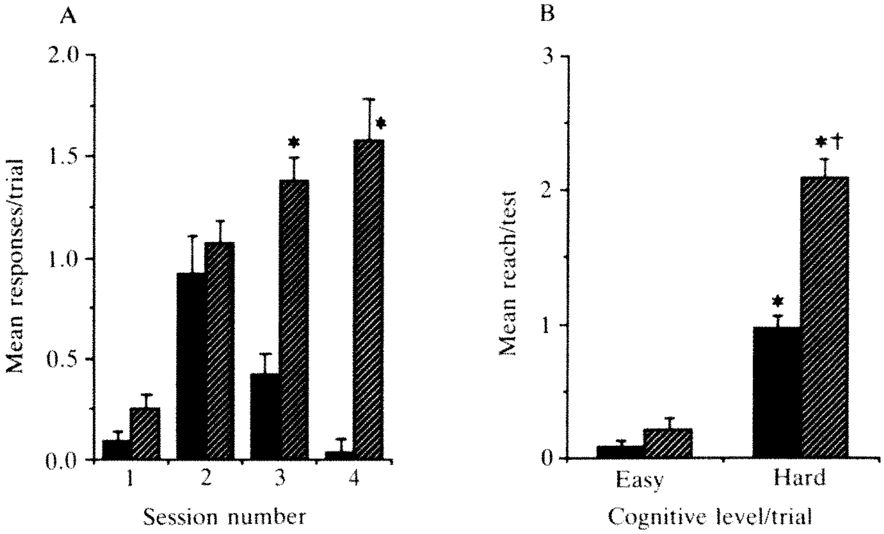

FIG. 7. Barrier reaches during acquisition (A) and barrier reaches shown by cognitive level (B). A, number of barrier reaches on the trials during the four acquisition sessions. On session 1 there were few opportunities to make barrier reaches and both groups of subjects made few barrier reaches. On session 3 and 4 MPTP-treated subjects made significantly ($P < 0.01$*) more barrier reaches than control subjects. B shows the number of barrier reaches made during acquisition testing on select trials designated easy or hard in terms of cognitive level. Both groups made significantly ($P < 0.01$*) more barrier reaches on hard trials than on easy trials and MPTP-treated subjects made significantly ($P < 0.01$†) more barrier reaches than control subjects only on the hard trials. Symbols as in fig. 4.

(F = 5.62, df 3,48, $P < 0.01$). Subjects in both groups made few barrier reaches on the easy trials and significantly more on the hard trials. MPTP-treated subjects made significantly more barrier reaches (mean of 2.0 per trial) than did control subjects only on the hard trials.

Significant increases in *perseverative responses* for MPTP subjects compared with controls (Group F = 8.12, df 1,16, $P < 0.01$) may also have added to increases in barrier reaching. There was an effect of the particular session on the frequency of perseveration (fig. 8) for all the subjects (Sessions F = 4.31, df 3,48, $P < 0.01$). There were very few opportunities to perseverate on the first session, more on the second and third sessions, and most on the final session. The significant increase in perseveration followed this pattern. MPTP-treated subjects made more perseverative responses on trials differentiated by motor difficulty (Group F = 11.09, df 1,16, $P < 0.01$ and Difficulty F = 7.41, df 3,48, $P < 0.01$). Subjects increased perseverative reaches on trials with a difficulty score of 9 and 12, which were also trials classified cognitively as hard. This was confirmed by the finding that all subjects perseverated more on hard than on the easy trials (Easy/Hard F = 11.41, df 3,48, $P < 0.01$).

MPTP-treated subjects made twice as many *awkward reaches* during the sessions as controls, shown in fig. 9 (Group F = 4.76, df 1,16, $P < 0.05$). When an awkward reach was made, the subject reached with the hand furthest from the opening of the box (when the opening was to the left or right side) which makes it difficult to retrieve

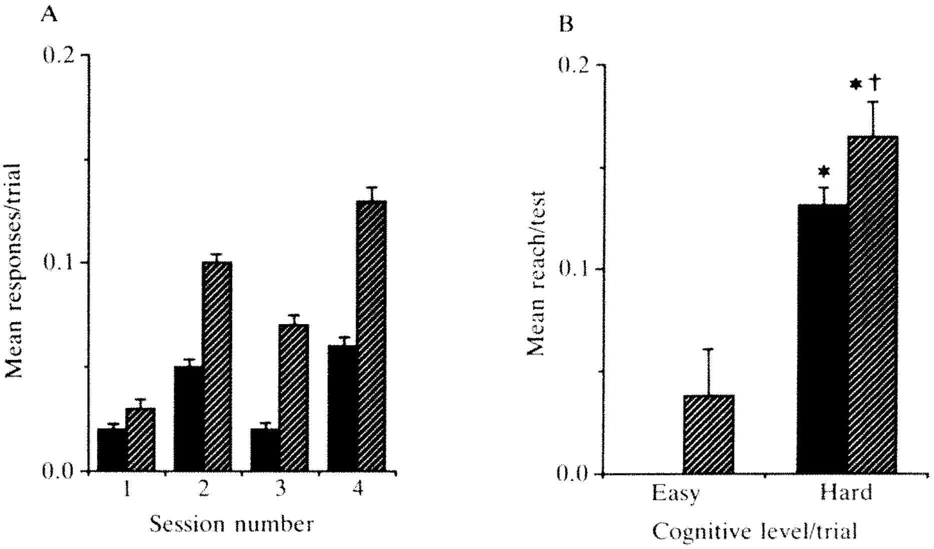

FIG. 8. Perseverative responses during acquisition (A) and perseverative reaches shown by cognitive level (B). A, number of perseverative reaches on the trials during the four acquisition sessions. MPTP-treated subjects made significantly ($P < 0.01$) more perseverative responses on all the sessions than control subjects. B shows the number of perseverative responses made during acquisition testing during select trials designated easy or hard in terms of cognitive level. Both groups made significantly ($P < 0.01$*) more perseverative responses on hard trials than on easy trials and MPTP-treated subjects made significantly ($P < 0.01$†) more perseverative responses than control subjects only on hard trials. Symbols as in fig. 4.

the reward. Awkward reaching was not related to a pre-existing handedness or hand preference, shown in fig. 9. There were no differences for the groups in the probability of responding with the right or left hand on the first reach of a trial or for the total number of reaches during a trial. The number of awkward reaches also varied with different difficulty scores, significantly on those with scores of 6 and 12 where the opening of the box faced away from the subjects and the reward was in the front corner (fig. 9). There were significant effects of Group (F = 12.07, df 1,16, $P < 0.01$) and Difficulty (F = 3.13, df 3,48, $P < 0.01$).

MPTP-treated subjects made significantly more *awkward reaches* on *easy* trials and on *hard* trials than did controls (Group F = 13.93, df 1,16, $P < 0.01$), shown in fig. 9. On the easy trials MPTP-treated subjects averaged 0.03 per trial compared with none for controls. On hard trials MPTP-treated subjects averaged 0.15 awkward reaches per trial compared with less than 0.05 for control subjects. The increase in the mean number of awkward reaches was not confined to the hard trials for the MPTP-treated subjects; both groups of subjects made more awkward reaches on the hard trials than on easy trials (Easy/Hard F = 6.53, df 3,48, $P < 0.01$).

DISCUSSION

Motor and cognitive impairments in the acquisition of an object retrieval task were found in monkeys 8–12 months after MPTP administration in the absence of grossly

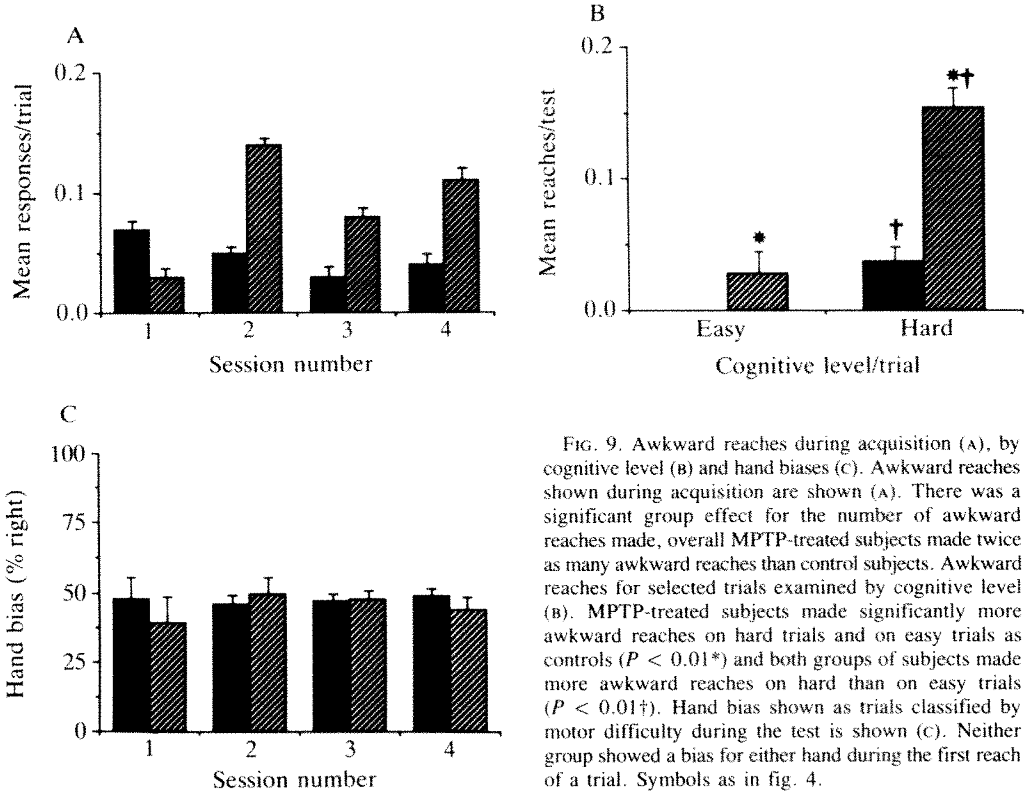

FIG. 9. Awkward reaches during acquisition (A), by cognitive level (B) and hand biases (C). Awkward reaches shown during acquisition are shown (A). There was a significant group effect for the number of awkward reaches made, overall MPTP-treated subjects made twice as many awkward reaches than control subjects. Awkward reaches for selected trials examined by cognitive level (B). MPTP-treated subjects made significantly more awkward reaches on hard trials and on easy trials as controls ($P < 0.01$*) and both groups of subjects made more awkward reaches on hard than on easy trials ($P < 0.01$†). Hand bias shown as trials classified by motor difficulty during the test is shown (C). Neither group showed a bias for either hand during the first reach of a trial. Symbols as in fig. 4.

observable motor impairments. MPTP-treated subjects consistently made fewer correct and successful responses on the test sessions than control subjects when learning the object retrieval task. Examination of the trials differentiated by cognitive level indicated that MPTP-treated subjects were worse on hard than on easy trials and were also worse than controls when the trials were hard. The behavioural deficits were accompanied by marked DA depletions, assessed by levels of HVA in cisternal CSF. The differences between MPTP-treated and control subjects in the execution of this object retrieval task will be discussed in terms of the cognitive and motor aspects, with reference to the role of the dopaminergic system in behaviour and in patients with idiopathic or MPTP-induced parkinsonism.

MPTP-treated subjects were found to have subtle motor impairments that could not be detected using gross observational measures. Marked differences in the number of motor problems were observed when results of the trials were examined to reflect the amount of motor difficulty inherent in the trial types. In contrast to control subjects, MPTP-treated subjects had more motor problems and made more overall reaches on higher-difficulty trials and had significantly increased motor problems compared with controls. Trials with high difficulty scores required the most skilled arm, hand and digit movement. Trials with a difficulty score of 1 and 2, in which the open side of the box faced the subjects, presented no problems for MPTP-treated or control subjects. Thus, when MPTP-treated subjects had only to reach directly in their line of sight, they did not have difficulty in retrieving the reward on the first reach. In monkeys, substantial improvements in MPTP-induced motor impairments have been reported in some studies, particularly those using lever-pulling tasks (Eidelberg *et al.*, 1986; Freed *et al.*, 1987), while other studies have failed to find significant recovery of function (Degryse and Colpaert, 1986); in humans, MPTP appears to produce permanent impairments (Langston *et al.*, 1983). Our findings raise the possibility that subtle motor deficits may be missed by using gross motor activity ratings and by using tasks that require the subject only to reach directly in front (such as pressing a lever), and indicate the sensitivity of this task to MPTP-induced motor deficits.

Like patients with Parkinson's disease (Tatton *et al.*, 1984; Rogers *et al.*, 1987), our MPTP-treated monkey/subjects were slower to initiate reaches than control subjects. Reach initiation times were five times that of controls on the final session. MPTP-treated subjects were slower than controls on trials that were rated cognitively as easy as well as hard. The longest latencies in MPTP-treated subjects were on the trials with the highest motor difficulty score. Therefore, response initiation latencies were affected both by the cognitive level of the trials and by the motor difficulty of the trials. Response initiation times have also been reported to be impaired during simple reaching tests in symptomatic monkeys after MPTP treatment (Doudet *et al.*, 1985; Schultz *et al.*, 1985).

MPTP-treated monkeys retrieved the object successfully when required to reach directly in their line of sight, but reached more often to the barrier when a detour required them to switch strategies or to increase movement complexity. MPTP-treated subjects made more than twice as many perseverative reaches on the second, third and final sessions than the control monkeys. Although both groups of subjects made more barrier and perseverative reaches on trials rated as cognitively hard, thereby confirming the a *priori* classifications of cognitive level, MPTP-treated subjects made significantly more of them on the hard trials than did control subjects. Parkinsonian, frontal lobe 'lesioned' and MPTP patients have been shown to have analogous cognitive impairments, characterized by an inability to inhibit response strategies and by deficits in planning responses. Indeed, in monkeys, lesions of the frontal lobe result in similar impairments on this task, such as an inability to inhibit reaching in their line of sight (Diamond and Goldman-Rakic, 1985; Diamond, 1989*b*).

In addition to exhibiting cognitive deficits measured by barrier reaches and perseverative responses, MPTP-treated subjects made awkward reaches (reaching more often than controls with their hand contralateral to the open side), also found after prefrontal cortex lesions (Diamond, 1989*b*). Awkward reaches did not appear to be due to a unilateral motor preference, since a *hand bias* or a *hand preference* were not observed in either of the groups. Both groups of subjects made more awkward reaches on trials that had a hard cognitive rating than on easy ones; however, MPTP-treated subjects showed increased awkward reaching on easy and hard trials compared with control subjects. Although it is more expeditious to reach with the hand closest to the opening of the box, subjects could still retrieve the reward. Nevertheless, awkward reaches suggest a deficit in response strategy and may be useful in determining response biases resulting from unilateral differences in DA levels.

DA depletion indicated by profound reductions in CSF HVA concentration suggests that the functional integrity of the DA system may be partially responsible for these behavioural impairments, even in subjects that do not show gross motor deficits. In addition, CSF HVA levels remained significantly decreased 8–12 months after MPTP administration. In other mildly affected MPTP-treated subjects, we found marked DA depletions in the brain, particularly in the caudate, putamen, substantia nigra and ventral tegmental area (Elsworth *et al.*, 1987*b*, 1989). These monkeys were also 'asymptomatic' by the same behavioural observation methods as the 6 monkeys in the present report. Regional DA reductions resulting from MPTP administration may therefore produce the deficits reported here; however, the precise pattern of MPTP-induced DA depletion in regions of cortex, caudate and putamen is not fully known. The cognitive and motor deficits measured during the acquisition of this task were reminiscent of disorders resulting from DA depletions, such as Parkinson's disease, damage to the frontal lobes, and more limited preliminary data on accidental MPTP toxicity in humans. The similarities of these deficits further supports the extent to which MPTP toxicity in primates is a model of Parkinson's disease.

Finally, this object retrieval task detects cognitive and motor deficits at levels of behavioural impairment that are below the threshold that would be detected by gross observation or by simple direct reaching or lever pulling tasks. Long-term studies with this type of task (Taylor *et al.*, 1990) will therefore be necessary to determine 'spontaneous' recovery after MPTP administration or after procedures alleged to restore dopaminergic function, such as grafts with adrenal, fetal neural, or other types of cells and tissue. We have reported (Taylor *et al.*, 1987) preliminary results on the attenuation of cognitive and motor deficits measured using this task after fetal dopaminergic substantia nigra grafts in MPTP-treated primates. More detailed studies, using similar tasks in human subjects known to have 'subthreshold' DA depletion would also be of interest for tracking and correlating with the course of possible effects of DA depletion. Similar studies in patients receiving tissue grafts would perhaps also be of value for studying the effects of possible recovery.

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THE AETIOLOGY OF TRANSIENT GLOBAL AMNESIA

A CASE-CONTROL STUDY OF 114 CASES WITH PROSPECTIVE FOLLOW-UP

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SUMMARY

A case-control comparison of 114 transient global amnesia (TGA) patients using both normal community-based controls (n = 109) and transient ischaemic attack (TIA) controls (n = 212) showed no evidence of an increased risk of TGA associated with any of the conventional risk factors for cerebrovascular disease. However, migraine was significantly more common in the TGA patients than in either control group. A prospective longitudinal study using actuarial (life table) analysis confirmed that the prognosis of the TGA patients was strikingly better than that of the TIA controls. An important minority (7%) of TGA cases developed epilepsy, usually within one year of presentation. On the basis of this evidence, a thromboembolic aetiology for TGA can be confidently rejected, at least for the vast majority of cases. There are good theoretical reasons to link migraine and TGA causally, and occasionally epilepsy may masquerade as TGA. In the remaining cases the cause remains unknown.

INTRODUCTION

Despite the fact that transient global amnesia (TGA) is now a well established clinical syndrome with an extensive literature covering more than 1000 cases, its aetiology remains an enigma. The most widely accepted view is that TGA is due to thromboembolic cerebrovascular disease (for review, *see* Logan and Sherman, 1983; Caplan, 1985). The supportive evidence for this claim, however, is contradictory; whereas some clinical studies have found a very high rate of vascular risk factors and of subsequent stroke (Mathew and Meyer, 1974; Shuping *et al.*, 1980; Jensen and Olivarius, 1981; Cattaino *et al.*, 1984; Kushner and Hauser, 1985), others have reported no increase in prevalence of such risk factors or subsequent strokes above that expected in the normal population (Nausieda and Sherman, 1979; Crowell *et al.*, 1984; Hinge *et al.*, 1986; Miller *et al.*, 1987). Some authors have advocated an epileptic cause (Tharp, 1969; Gilbert, 1978; Rowan and Protass, 1979; Fisher, 1982) and strong aetiological claims have been made for migraine (Olivarius and Jensen, 1979; Caplan *et al.*, 1981; Crowell *et al.*, 1984). In addition, single cases have been reported in association with a wide range of conditions including brain tumours (e.g., Aimard *et al.*, 1971; Lisak and Zimmerman, 1977; Meador

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et al., 1985), drug overdosage (Gilbert and Benson, 1972; Greenlee *et al.*, 1975), polycythaemia (Matias-Guiu *et al.*, 1985) and intracerebral and subarachnoid haemorrhage (Landi *et al.*, 1982; Sandyk, 1984). The cause of this aetiological uncertainty appears to be threefold: first, variation in the use of the term TGA and the lack of generally agreed diagnostic criteria; secondly, inadequacy of data collection in the majority of the reported clinical and epidemiological studies, which have relied upon retrospective methods; and thirdly, and most importantly, lack of control data in all but one of the reported studies.

The term TGA was introduced by Fisher and Adams (1958, 1964) to describe a clinical syndrome, characterized by the abrupt onset of severe anterograde amnesia, usually accompanied by repetitive questioning, which occurred in the middle-aged or elderly. During the attack the patients remained alert and communicative, and personal identity was preserved. Focal neurological and epileptic features were absent, and general cognition appeared intact. After a number of hours the ability to lay down new memories gradually recovered and subjects returned to normal except for a dense amnesic gap for the duration of the attack. It should be stressed that the original authors were highly restrictive in their use of the diagnosis. Subsequently, however, the term has been applied to a variety of different clinical situations merely sharing the feature of prominent memory loss. Until recently the majority of authors have given no criteria at all. In keeping with the criteria proposed by Caplan (1985), we reserve the term TGA for witnessed attacks of definite amnesia without disturbance of consciousness, focal neurological symptoms or epileptic features in patients who do not have active epilepsy and have not sustained a recent head injury, and which resolve within 24 h.

Since TGA is most common in the elderly, many of the patients will have coincident vascular risk factors and will suffer major vascular events (stroke and myocardial infarction) purely by chance. To establish whether TGA is associated with risk factors for cerebrovascular disease (CVD) there is a need for properly controlled studies, ideally comparing cases with both normal controls and controls with conventional transient ischaemic attacks (TIAs). To date there has been only one small case-control study of TGA. In this Kushner and Hauser (1985) compared 18 TGA cases with hospital-based normal controls. They found a significant increase in the prevalence of vascular risk factors. However, their findings were contrary to those of two recently reported large uncontrolled studies (Hinge *et al.*, 1986; Miller *et al.*, 1987). There have been no reported series comparing TGA cases with TIA controls.

We have attempted to address these deficiencies in the literature and to investigate the aetiology and natural history of TGA by means of a case-control study. The specific objectives of our study were to measure the prevalence of various putative risk factors in a well defined TGA population and to compare these with two control populations—normal community-based controls and conventional TIA controls—and to compare the outcome in the TGA and TIA groups. If the commonly held hypothesis that TGA represents a variety of thromboembolic CVD is correct, then there should be *no* difference in the prevalence of vascular risk factors, or in outcome between TGA patients and those with conventional TIAs, but there should be significant differences between TGA patients and normal controls. By contrast, if TGA is unrelated to CVD there should be significant differences in vascular risk factor prevalence and outcome between TGA and TIA cases and *no* difference between TGA and normal controls.

SUBJECTS AND METHODS

Diagnostic criteria for TGA

(1) Attacks must be witnessed and information available from a capable observer who was present for most of the attack. (2) There must be clear-cut anterograde amnesia during the attack. (3) Clouding of consciousness and loss of personal identity must be absent, and the cognitive impairment limited to amnesia (i.e., no aphasia, apraxia, etc.). (4) There should be no accompanying focal neurological symptoms or signs, and epileptic features must be absent. (5) Attacks must resolve within 24 h. (6) Patients with a recent head injury or known active epilepsy (i.e., remaining on medication or one seizure in the past 2 yrs) are excluded.

Ascertainment of TGA cases

The 114 cases included in the case-control study were collected by two methods. (1) Fifty-one cases were ascertained after reviewing all possible cases seen in the Department of Neurology in Oxford between 1977 and 1984. These 51 have been designated the *retrospective group*. Comprehensive data were available on all cases comparable with that on the prospective group. A further 18 were excluded for the reasons given in Table 1. All patients were interviewed in 1984 and their general practitioners were also contacted to provide information on any amnesic attacks, vascular events and other medical problems after their presentation with TGA. From 1984 until 1987 all were kept under regular follow-up as described below. (2) Sixty-three cases constituted the *prospective group* and were collected between 1984 and July 1987. Before the commencement of the prospective study we wrote to all general practitioners in the Oxfordshire Region informing them of the study and asking them to refer any *potential* cases of TGA. The consultant neurologists at the Radcliffe Infirmary and the Oxfordshire Community Stroke Project also participated in the study. In total 84 patients were referred for assessment, all of whom were seen by one of the authors (J.H.); 21 were excluded for the reasons shown in Table 1.

TABLE 1. REASONS FOR EXCLUSION OF PATIENTS FROM THE DEFINITE TGA CATEGORY

	Retrospective group	*Prospective group*
Definite TGA cases	51	63
Non-TGA cases	18	21
Reasons for exclusion		
Unwitnessed attacks	7	7
Limited or very poor details	3	5
Other neurological features	7	7
Following head injury	0	1
Known active epilepsy	1	1
Total cases (definite TGA and non-TGA cases)	69	84

We initially separated the prospective and retrospective groups in order to ensure that there were no significant differences between the groups and that they could therefore be combined for the case-control study.

Clinical assessment

All prospective cases together with family members (or other informants) underwent a semistructured interview. The following information was collected: demographic data; details of attack including duration, potential precipitating factors within the preceding 24 h (e.g., swimming, sexual intercourse, medical procedures, physical exertion or emotional stress) and accompanying neurological features; past medical history, notably ischaemic or structural heart disease, CVD, diabetes mellitus, peripheral vascular disease, migraine, epilepsy; smoking history and alcohol consumption; and family history. All cases underwent a standard clinical examination, looking particularly for evidence of vascular disease. The following investigations were performed after the attack whenever possible: full blood count and ESR, fasting blood lipids and glucose, electrocardiogram (ECG), chest x-ray, electroencephalogram (EEG) and a CT scan of the head.

Follow-up of the cases

All prospectively ascertained patients were reviewed at 6 months after the attack. Thereafter follow-up was by postal questionnaire 6 monthly. Similarly, all retrospectively ascertained cases were kept under 6 monthly postal review. Any patient reporting significant medical problems was seen and their general practitioner was contacted for further medical details. Information was available in all cases; none has been lost to follow-up.

Normal community-based controls

For each index (TGA) patient we selected a control of the same sex and age (±2 yrs) from the age/sex registers of two Oxford general practices. The nearest names (alphabetically) were taken. No other selection criteria were applied. A letter requesting the subjects' help was then sent to those selected. All willing participants were interviewed and examined by J.H., and the same data as for the TGA cases thereby obtained. The response rate for the first choice subjects was 59%. We then selected alternative second and if necessary third choice names by the same method. Overall, 200 subjects were approached. The final community-based control group consisted of 109 subjects, 70 men and 39 women, with a mean age of 65.4 (SD 8.5) yrs. The age distribution is shown in fig. 1.

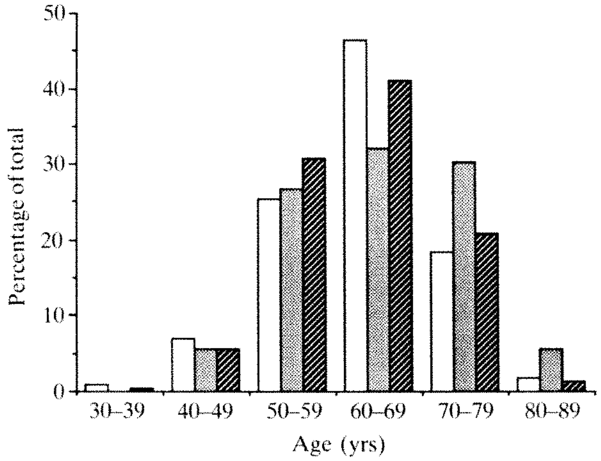

FIG. 1. Age distribution of the TGA cases (n = 114, open columns), normal community-based controls (n = 109, dotted columns) and TIA controls (n = 212, hatched columns).

Transient ischaemic attack controls

For each index (TGA) patient, 2 age and sex-matched TIA cases were selected from the personal records of one of the authors (C.P.W.). The cases were selected from a data base of approximately 500 (mainly hospital referred) TIA cases on whom comprehensive demographic, clinical, risk factor and laboratory data were available. All the cases had been kept under regular follow-up review either personally, or by postal questionnaire to the patients and their general practitioners. The TIA controls were also matched for year of presentation, so that the length of follow-up of the TGA and TIA groups would be approximately equivalent. Only patients presenting after TIAs who had not had a prior major stroke were chosen: 228 cases were thus selected, but after review 16 were excluded because of inadequate information or limited follow-up. The final TIA control group consisted of 212 cases, 122 men and 90 women with a mean age of 62.4 (SD 8.8) yrs. The age distribution is shown in fig. 1. The presenting disorder was amaurosis fugax in 66 and transient cerebral ischaemia in 146.

Definitions

A *transient ischaemic attack (TIA)* was defined as an acute loss of focal cerebral or ocular function, with symptoms lasting less than 24 h and which after adequate investigation was thought to be due to embolic or thrombotic vascular disease (Warlow and Morris, 1982). A *stroke* was defined in accordance with the WHO guidelines as a focal neurological deficit (with the exception of cases of subarachnoid haemorrhage) of presumed vascular origin lasting for more than 24 h or leading to death (Hatano, 1976). In addition, cases with acute ocular vascular events lasting 24 h or more were included. A *myocardial infarction* was diagnosed only if confirmed by acute ECG, enzyme changes or postmortem examination. *Deaths* were categorized as either (1) vascular (stroke, myocardial infarction, abdominal or thoracic aneurysm rupture, or sudden death of presumed vascular origin), or (2) nonvascular (all others). A *major vascular event* was defined as either a nonfatal stroke, nonfatal myocardial infarct or a vascular death.

Statistical methods

Proportions are quoted with 95% confidence intervals (95% CI) as described by Gardner and Altman (1986). In the case-control study an estimate of relative risk for each of the defined potential risk factors was obtained by calculating the odds ratio (OR) with 95% CI. If the 95% CI included 1.0 the difference between the groups was considered to be nonsignificant at the 5% level (Morris and Gardner, 1988). For the longitudinal study, vascular event/mortality rates were adjusted for length of follow-up for the group and expressed per 100 000 patient yrs. Outcome was assessed using actuarial (life table) methods based on Kaplan Meier survival curves and statistical analysis was by standard log rank tests of time to the first event, using two-tailed *P* values (Peto *et al.*, 1977).

RESULTS

Details of the TGA cases

A comparison of the retrospective and prospective TGA groups revealed no significant or major differences in the demographic data, clinical details, risk factor prevalence, laboratory data, and natural history. They were therefore combined into a single group of 114 cases. The clinical details of these cases are described in detail elsewhere (Hodges, 1988). Briefly, the mean age was 62.3 (SD 8.5, range 39–82) yrs; the age distribution is shown in fig. 1. There were 69 men and 45 women. The vast majority (85%) were seen after a single attack. The mean duration of amnesia was 4.2 (SD 2.8) h. Potential precipitating factors were reported in the preceding 24 h by a substantial number of cases; 3% followed immediately after swimming in cold water, 3% occurred after intercourse, 3% had had medical procedures, 18% followed unusually severe physical

TABLE 2. COMPARISON OF RISK FACTOR PREVALENCE*

	Prevalence				
	No.	*%*	*(95% CI)*	*OR*	*(95% CI)*
Hypertension					
At any time					
TGA	25	21.9	(14–30)		
Normal controls	33	30.3	(22–39)	1.5	(0.8–3.3)
TIA controls	81	38.2	(32–45)	2.2	(1.3–3.8)
Currently on treatment					
TGA	20	17.5	(10–25)		
Normal controls	28	25.7	(18–34)	1.6	(0.8–3.3)
TIA controls	69	32.5	(26–39)	2.3	(1.3–4.0)
Treatment**					
TGA	42	36.8	(28–36)		
Normal controls	39	35.8	(27–45)	1.0	(0.1–35)
TIA controls	108	50.9	(44–58)	1.8	(1.1–2.9)
Treatment***					
TGA	55	48.2	(39–57)		
Normal controls	50	45.9	(36–55)	0.9	(0.4–2.1)
TIA controls	134	63.2	(57–70)	1.8	(1.1–3.0)
Ischaemic heart disease[1]					
TGA	8	7.0	(2–12)		
Normal controls	17	15.6	(9–22)	2.4	(0.9–6.4)
TIA controls	57	26.9	(21–33)	4.9	(2.3–10)
Structural heart disease[2]					
TGA	8	7.0	(2–12)		
Normal controls	15	13.8	(7–20)	2.1	(0.8–5.9)
TIA controls	36	17.0	(12–22)	2.7	(1.2–6.2)
Atrial fibrillation[3]					
TGA n = 103	3	2.9	(0.2–6)		
Normal controls		Not available			
TIA controls	7	3.3	(0.9–6)	1.1	(0.2–5.7)
All arrhythmias[4]					
TGA n = 103	3	2.9	(0.2–6)		
Normal controls		Not available			
TIA controls	11	5.2	(2–8)	1.8	(0.3–12)
Cerebrovascular disease[5]					
TGA	7	6.1	(2–10)		
Normal controls	8	7.3	(2–12)	1.2	(0.1–100)
TIA controls		Not applicable			
Cervical bruits					
TGA	10	8.8	(4–14)		
Normal controls	10	9.2	(4–15)	1.0	(0.5–2.2)
TIA controls	64	30.2	(24–36)	4.5	(2.2–9.0)
Peripheral vascular disease					
TGA	4	3.5	(0.1–7)		
Normal controls	2	1.8	(0.1–4)	0.5	(0.1–20)
TIA controls	32	15.1	(10–20)	4.9	(1.7–14)
Diabetes mellitus					
TGA	2	1.8	(0.1–4)		
Normal controls	3	2.8	(0.1–6)	1.6	(0.1–100)
TIA controls	8	3.8	(1.2–6)	2.2	(0.2–22)
Smoking					
At any time					
TGA	56	49.1	(40–58)		
Normal controls	67	61.5	(52–71)	1.6	(0.9–2.9)
TIA controls	159	75.0	(69–81)	3.1	(1.9–5.0)
Current: cigarettes					
TGA	17	15.6	(9–22)		
Normal controls	22	20.2	(13–28)	1.4	(0.6–3.3)
TIA controls	84	39.6	(33–46)	3.7	(2.1–6.7)

Current: pipe or cigars					
TGA	8	7.0	(2–12)		
Normal controls	11	10.1	(4–16)	1.4	(0.4–5.7)
TIA controls	13	6.1	(3–9)	0.8	(0.1–40)
Polycythaemia[6]					
TGA n = 112	6	5.4	(1–10)		
Normal controls		Not available			
TIA controls	26	12.3	(8–17)	2.5	(0.9–6.6)
Hypercholesterolaemia[7]					
TGA n = 93	18	19.4	(11–27)		
Normal controls		Not available			
TIA controls	36	17.0	(12–22)	0.8	(0.3–2.2)
Alcohol intake					
>20 units/week					
TGA	15	13.2	(8–20)		
Normal controls	9	7.8	(3–13)	0.6	(0.2–1.7)
TIA controls	20	9.4	(5–13)	0.7	(0.3–1.6)
Epilepsy					
TGA	3	2.6	(0.1–6)		
Normal controls	3	2.8	(0.1–6)	1.0	(0.8–1.3)
TIA controls		Not available			
Migraine					
Any type					
TGA	34	29.8	(21–38)		
Normal controls	19	17.4	(10–24)	0.5	(0.2–0.9)
TIA controls	43	20.3	(15–26)	0.6	(0.3–0.9)
Classical					
TGA	26	22.8	(15–30)		
Normal controls	12	11.0	(5–17)	0.4	(0.2–0.9)
TIA controls	31	14.6	(10–19)	0.6	(0.3–1.0)
Fulfilling research criteria[8]					
TGA	28	24.6	(17–32)		
Normal controls	13	11.9	(6–18)	0.4	(0.2–0.9)
TIA controls		Not available			

* The TGA cases (n = 114 unless stated otherwise) are compared with the normal controls (n = 109) and with the TIA controls (n = 212) by odds ratio with 95% confidence intervals (OR 95% CI); 95% CI that include 1.0 are not statistically significant at the $P < 0.05$ level. ** Currently on treamtent for hypertension, or found to have a systolic BP ≥ 180 and/or a diastolic BP ≥ 100. *** Currently on treatment for hypertension, or found to have a systolic BP ≥ 160 and/or a diastolic BP ≥ 95. [1] Angina or proven myocardial infarction. [2] Includes patients with diastolic murmurs, systolic murmurs of > 2/4 intensity, congenital heart disease or cardiomyopathy. [3] ECG proven. [4] Atrial fibrillation or flutter, sinoatrial disease, atrioventricular block or ventricular arrhythmias. [5] Past stroke or TIA. [6] Haematocrit > 50 ml/dl. [7] Cholesterol > 2.8 g/l. [8] Blau (1984).

exertion, and 14% reported emotionally stressful events such as witnessing a vehicle accident, giving evidence in court, receiving news of serious family illness, and attending a funeral. During the attack 10% complained of headache and a similar proportion were nauseated. When examined after the episode, no significant neurological signs were detected. CT scans were performed on 95 patients; a small number showed minor atrophic changes, but no instances of brain tumour, cerebral infarction (unexplained by previous damage) or haemorrhage were found.

Estimated minimum incidence of TGA

We were able to assess the minimum incidence using the Oxfordshire Community Stroke Project (OCSP) data. Between November 1, 1981 and October 31, 1987 all potential cases of CVD (TIA and stroke) from the defined study population of 105 000 were assessed by the OCSP (Bamford *et al.*, 1988). Of the 512 patients referred with transient symptoms suggesting a possible diagnosis of TIA only 195 were confirmed as TIAs; 17 of those excluded had a diagnosis of TGA. All 17 were included in our study. Since these cases were from a defined population we were able to calculate a minimum annual incidence of 3.4 per 100 000 (95% CI 0.1–6.9).

Risk factor prevalence

The prevalence of risk factors in the index group, normal controls and TIA control groups is shown in Table 2. Figs 2 and 3 illustrate the odds ratios and 95% CI (OR 95% CI) comparing the index group with each of the control groups.

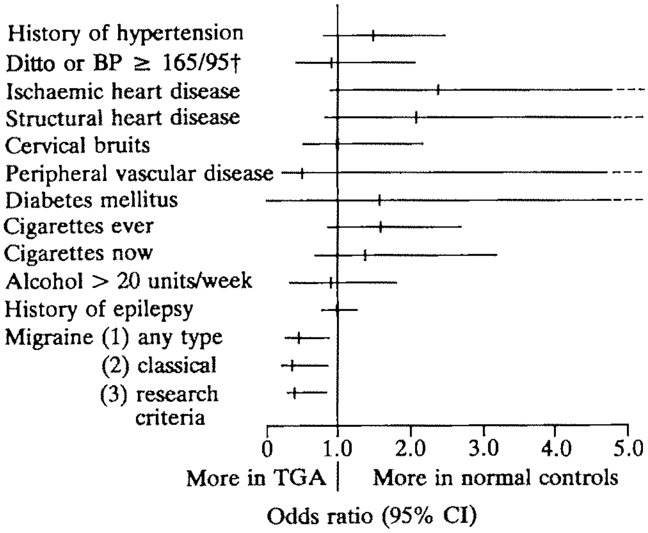

FIG. 2. Comparison of the prevalence of risk factors in the TGA cases (n = 114) and the normal controls (n = 109) showing the odds ratio (OR, vertical bars) and the 95% CI (horizontal bars). An OR of <1.0 indicates that the risk factor was more prevalent in the TGA group and an OR of >1.0 indicates that it was more prevalent in the normal control group. If the 95% CIs include 1.0 the difference between the groups was not statistically significant at the $P = 0.05$ level. † History of hypertension or found to have a BP recording of 165/95 or greater.

TGA cases versus normal controls. The only factor significantly associated with an *increased* risk for TGA compared with normal controls was migraine. There was no altered risk associated with hypertension, ischaemic or structural heart disease, atrial fibrillation, arrhythmias, diabetes, peripheral vascular disease, cervical bruits, smoking, alcohol consumption or epilepsy.

TGA cases versus TIA controls. The only factor significantly associated with an *increased* risk for TGA compared with TIA was migraine. The following factors were associated with a significantly *reduced* risk for TGA compared with TIA: hypertension, ischaemic and structural heart disease, cervical bruits, cigarette smoking (past and present)

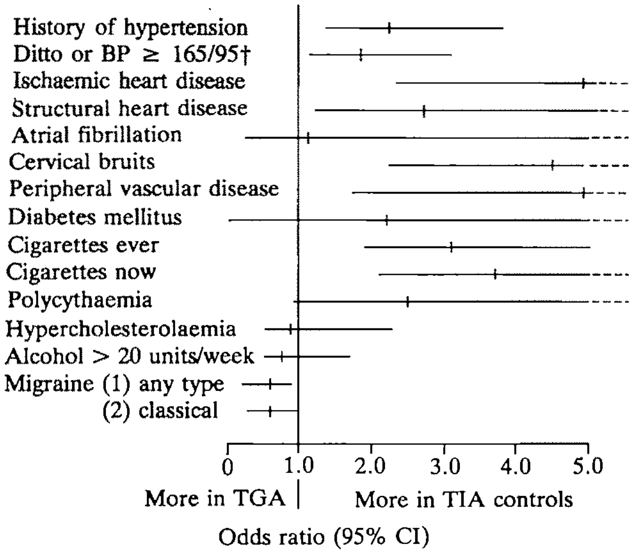

FIG. 3. Comparison of the prevalence of risk factors in TGA cases (n = 114) and the TIA controls (n = 212) showing the odds ratio (OR, vertical bars) and the 95% CI (horizontal bars). An OR of <1.0 indicates that the risk factor was more prevalent in the TGA group and an OR of >1.0 that it was more prevalent in the TIA group. If the 95% CIs include 1.0 then the difference between the groups was not statistically significant at the $P = 0.05$ level. † History of hypertension or found to have a BP recording of 165/95 or greater.

and peripheral vascular disease. There was no altered risk associated with atrial fibrillation, diabetes, pipe or cigar smoking, polycythaemia, hypercholesterolaemia or alcohol consumption.

Longitudinal comparison of TGA and TIA groups

The total length of follow-up for the TGA group was 326 yrs and for the TIA group, 732 yrs. Since the mean length of follow-up of the TIA controls (42.0±27.4 months) was significantly longer than the TGA cases (34.8±27.2 months) ($t = 2.28$, $P < 0.05$), it was important to compare standardized vascular event and mortality rates and to analyse outcome using actuarial methods. Table 3 compares the number of events per group. The incidence data (per 100 000 patient yrs) are shown in Table 4.

Deaths. In the TGA group of 114 patients only 2 deaths occurred, both due to nonvascular causes (1 multiple myeloma, 1 prostatic carcinoma). By contrast, in the TIA group of 212 patients there were 33 deaths, 21 due to vascular causes (5 strokes, 13 myocardial infarction, 3 sudden death of presumed vascular origin). The standardized mortality was 7.4 times greater in the TIA controls than in the TGA cases. Kaplan Meier analysis of survival (fig. 4) indicated a significant difference between the groups ($P = 0.0006$). The excess mortality in the TIA group was due entirely to vascular causes: the difference in vascular mortality (excluding patients dying from nonvascular causes) was highly significant ($P = 0.004$), whereas there was no difference between the groups for nonvascular deaths ($P = 0.23$).

TABLE 3. COMPARISON OF THE NUMBER OF VASCULAR EVENTS AND DEATHS DURING FOLLOW-UP IN THE TGA CASES AND TIA CONTROLS

	TGA cases (*n = 114*)	*TIA controls* (*n = 212*)
Events		
Stroke (fatal and nonfatal)	2	32
TIA	4	32
Myocardial infarction (fatal and nonfatal)	0	16
Deaths:		
All	2	33
Vascular	0	21
Nonvascular	2	12
Stroke, MI or vascular death	2	49

TABLE 4. COMPARISON OF THE VASCULAR EVENT INCIDENCE AND MORTALITY RATE (PER 100 000 PATIENT YRS OF FOLLOW-UP) IN THE TGA CASES AND TIA CONTROLS

	TGA cases *n = 114*	*TIA controls* *n = 212*	*Ratio* *TIA/TGA*
Events			
Stroke (fatal and nonfatal)	613	4374	7.1
TIA	1226	4374	3.6
Myocardial infarction (fatal and nonfatal)	0	2187	–
Deaths			
All	613	4511	7.4
Vascular	0	2869	–
Nonvascular	613	1639	2.7
Stroke, MI or vascular death	613	6698	10.9

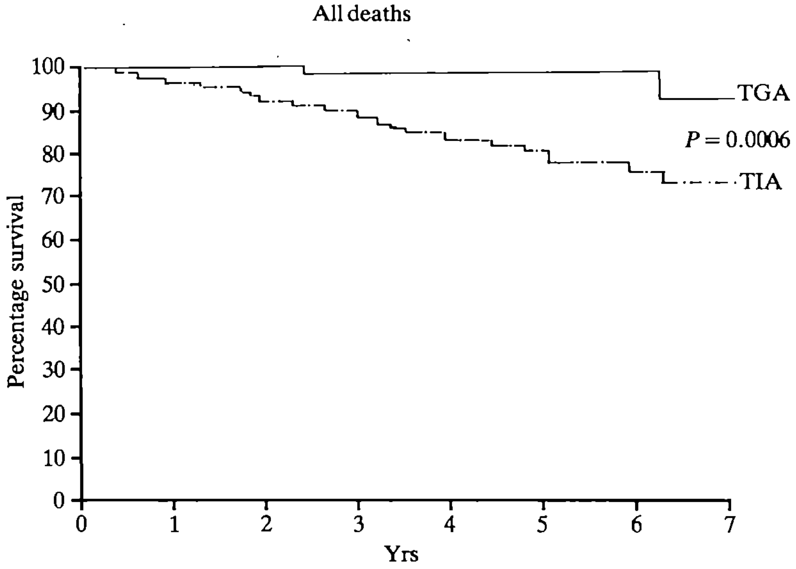

FIG. 4. Kaplan Meier survival curves (until death) comparing the TGA cases and the TIA controls.

Vascular events. Strokes occurred during follow-up in 2 of the TGA patients (1 minor left hemisphere infarct at 26 months post-TGA, 1 retinal artery occlusion at 16 months post-TGA). By contrast, 32 of the TIA controls suffered strokes (29 nonfatal). When standardized for length of follow-up, the stroke incidence was 7.1 times greater in the TIA controls than the TGA cases. Kaplan Meier curves for survival free from stroke (excluding patients who died of causes other than stroke) showed a difference at the $P = 0.0002$ level (*see* fig. 5).

There were no cases of myocardial infarction in the TGA group, whereas 16 of the TIA controls sustained myocardial infarcts (5 nonfatal). Kaplan Meier analysis of survival free from myocardial infarction (excluding those patients who died from noncardiac causes) confirmed a highly significant difference between the groups ($P = 0.002$).

When fatal and nonfatal vascular events were combined, the difference between the groups was even more striking. During the period of follow-up almost a quarter of the TIA control group (49 of 212, 23.1%) had either a stroke, a myocardial infarct or died from vascular causes. By contrast, only 2% (2 of 114) of the TGA patients had such an event. The standardized incidence of major vascular events was 10.9 times higher in the TIA group, and actuarial analysis of survival free from a major vascular event (excluding those dying from nonvascular causes) confirmed a highly significant difference between the groups ($P = 0.0001$) (*see* fig. 6).

Epilepsy. During follow-up 8 of the 114 patients (7.0%) became overtly epileptic despite the strict inclusion criteria for TGA used in this study. The annual rate of epilepsy development was 2.5%, but as virtually all patients manifesting epilepsy did so within 12 months, the rate for the first year of follow-up was approximately 7%. None of

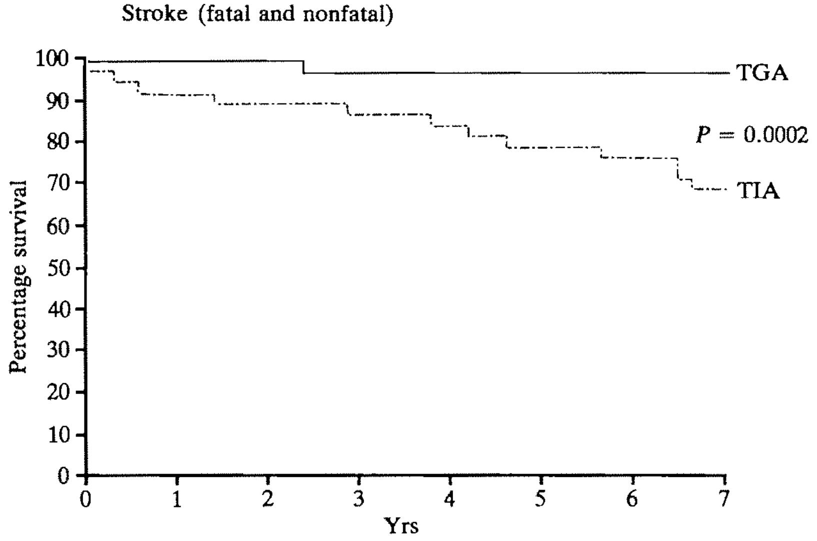

FIG. 5. Kaplan Meier survival curves for survival free from stroke (excluding nonstroke deaths) comparing the TGA cases and TIA controls.

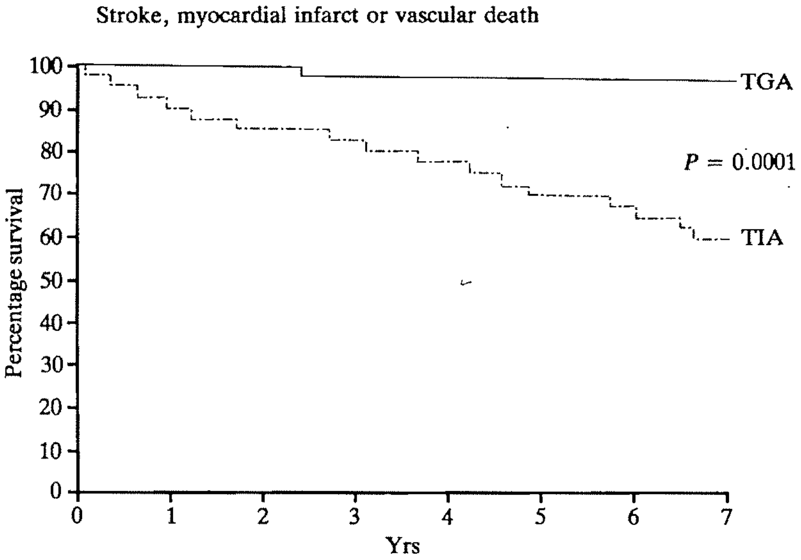

FIG. 6. Kaplan Meier survival curves for survival free from stroke, myocardial infarct or sudden death (excluding nonvascular deaths) in the TGA cases and TIA controls.

these patients had a history of epilepsy before their first attack of amnesia. Seven of the 8 cases of epilepsy were of complex partial type. The other patient developed major generalized seizures. CT brain scans were normal and routine EEG recordings after the presenting TGA episode were unremarkable in all cases. None of the TIA controls developed epilepsy.

DISCUSSION

The results of the case-control and longitudinal studies do not support a cerebrovascular aetiology for TGA. The epidemiological evidence for this conclusion is threefold. First, there were no significant differences in the prevalence of vascular risk factors between the TGA group and the matched (community-based) normal controls. In other words, there was no evidence of altered risk for TGA attributable to the factors associated with thromboembolic cerebral ischaemia, notably hypertension, ischaemic heart disease, structural heart disease, peripheral vascular disease, arrhythmias, cigarette smoking and polycythaemia. Secondly, there were significant differences in the prevalence of these risk factors between the TGA group and the matched TIA controls, such that analysis of relative risk (odds ratio) indicated a negative risk associated with a number of these factors compared with TIA. Thirdly, the follow-up comparison of the TGA and TIA groups revealed very significant differences in the incidence of vascular events and mortality. On the basis of this combined evidence a cerebrovascular aetiology for TGA can be confidently rejected as the cause of the majority of cases although, of course, it remains a possible explanation for some cases. By contrast, migraine was found to be more common in the TGA patients than either of the control groups and therefore appears to be a significant risk factor for TGA. In an important minority of cases epilepsy may initially masquerade as TGA.

Before discussing the implications of these results it is important to consider whether the TIA controls selected for this study were a representative sample. The risk factors for TIA are essentially the same as those for ischaemic stroke, and although the prevalence reported in studies of TIA patients has varied considerably, in general it is in keeping with that found in our TIA population (e.g., Schoenberg *et al.*, 1980; de Bono and Warlow, 1981; Harrison *et al.*, 1982). Furthermore, the 3 yr mortality following TIA found in the present study (14%) was very similar to that reported in other longitudinal studies (Cartlidge *et al.*, 1977; Simonsen *et al.*, 1981; Muuronen and Kaste, 1982).

It is also pertinent to consider whether the TIA patients used were the ideal cerebrovascular control group for the case-control study. Relevant to this issue is the site of putative pathology in TGA. Clinicopathological studies in patients with permanent amnesia have identified where damage must occur to produce selective severe memory loss—the medial temporal region (with an emphasis on the hippocampus) and diencephalic structures (for reviews, *see* Parkin, 1984; Squire, 1986). Since these structures receive their blood supply from the posterior cerebral circulation it could be argued that the ideal control group would be patients with purely vertebrobasilar TIAs. We considered using such a group, but as patients with vertebrobasilar TIAs constitute no more than 20–30% of TIA cases (Cartlidge *et al.*, 1977; Simonsen *et al.*, 1981) it would have been impractical to obtain a sufficiently large group for the study. In any case, there is no definite evidence that the prognosis following vertebrobasilar TIAs is different from carotid territory TIAs. Early studies suggested that they might have a better outcome, but more recent studies employing actuarial methods to analyse survival have found no differences in mortality or stroke incidence (Cartlidge *et al.*, 1977; Simonsen *et al.*, 1981).

The major findings of the present study were in keeping with the two large uncontrolled follow-up studies of TGA patients reported from the Mayo Clinic (Miller *et al.*, 1987) and from Denmark (Hinge *et al.*, 1986) in which selection criteria virtually identical to those used in our study were applied. In both of these studies the prevalence of vascular risk factors was low and the rate of subsequent stroke no higher than that expected in the local community. These authors also concluded that TGA is not due to CVD.

The results of our study were, however, contrary to the only other case-control study of TGA (Kushner and Hauser, 1985). The latter study included only 18 patients; two-thirds had a prior history of CVD, hypertension was 'present in the majority' and a half had symptoms of atherosclerotic heart disease. The prevalence of all these risk factors was significantly greater in the TGA group than in the controls. Their patient group appears to have been exceptional. In the Mayo Clinic study (Miller *et al.*, 1987), of 277 cases only 3% had suffered a TIA or stroke before their amnesic episode, and in the Danish series 5% had such a history. Similarly, the prevalence of ischaemic heart disease and hypertension was substantially lower in these two series than in that of Kushner and Hauser. One potential reason for this difference in the prevalence of risk factors is the definition of TGA; Kushner and Hauser included patients with additional focal neurological features during the attack such as ataxia, hemiparesis or facial palsy. Another potential area of bias in this study resulted from their selection of controls. It seems likely that their control group—elderly patients undergoing inpatient investigation for 'extra-axial neurological disorders'—would be healthier than an unselected community sample of the same age.

There have been relatively few follow-up studies of TGA patients and none has included a control group. Table 5 shows the available follow-up stroke rates converted into standardized stroke incidence rates/100 000 patient yrs of follow-up. It can be seen that rates differ by a factor of 10 between studies. The higher rates derive from studies of small patient groups. For instance, Mathew and Meyer (1974) followed up only 14 patients of whom 2 had subsequent strokes, a rate of 5714/100 000 patient yrs, whereas the recent large Mayo Clinic (Miller *et al.*, 1987) and Danish studies (Hinge *et al.*, 1986) found stroke incidence rates very close to that in the present study (613/100 000).

TABLE 5. STROKE INCIDENCE RATES CALCULATED FROM STUDIES REPORTING SYSTEMATIC FOLLOW-UP DATA

	No. of cases	*No. of strokes*	*Yrs of follow-up*	*Strokes/ 100 000 patient yrs*
Mathew and Meyer (1974)	14	2	35	5714
Nausieda and Sherman (1979)	43	0	123	–
Shuping *et al.* (1980)	41	2	165	1212
Jensen and Olivarius (1981)	28	9	170	5294
Cattaino *et al.* (1984)	30	0	27	–
Kushner and Hauser (1985)	18	0	42	–
Hinge *et al.* (1986)	74	3	415	723
Miller *et al.* (1987)	277	11	1700	647
Present study	114	2	326	613

If TGA is not due to thromboembolic CVD then what evidence is there to support other aetiologies? In the present study an important minority (7%) developed overt epilepsy, usually of temporal lobe type, typically within the first 12 months of follow-up. Presumably their presenting attacks were seizures in which the brief epileptic features went unnoticed by the patient or witnesses, and in which amnesia was the predominant feature. Previous follow-up studies of TGA patients have not revealed such a high rate of subsequent epilepsy (Mathew and Meyer, 1974; Nausieda and Sherman, 1979; Jensen and Olivarius, 1981; Cattaino *et al.*, 1984; Kushner and Hauser, 1985; Hinge *et al.*, 1986; Miller *et al.*, 1987). As case ascertainment in these studies was retrospective it is conceivable that patients who later developed epilepsy were excluded from the series because it was decided that their original attack could not have been a true TGA. This explanation seems likely, as the prevailing 'zeitgeist' favours CVD and not epilepsy as the aetiological factor in TGA. Clearly not all cases of TGA are due to epilepsy, but the same indistinguishable clinical phenomenon may arise following complex partial seizures.

Migraine was the only factor studied that was positively associated with TGA. However, this is a difficult area as there are no generally accepted criteria for the diagnosis of migraine. In an attempt to overcome this problem we used a range of definitions of increasing specificity. First, patients were simply asked if they suffered from migraine, as diagnosed at any time by a doctor and this diagnosis was accepted at face value. Then a clinical judgement was made to determine whether to classify the migraine as either classical or common. Finally, the research criteria proposed by Blau (1984) were applied. By all criteria the prevalence of migraine was greater in TGA than in either control group. As not more than a third of the TGA cases were migraineurs it is difficult to postulate that migraine is the direct cause in the majority of cases. The association does, however, suggest a causal role for migraine, at least in some patients. Previous authors have drawn attention to this association (Gilbert and Benson, 1972; Laplane and Truelle, 1974; Olivarius and Jensen, 1979). Caplan *et al.* (1981) argued that many of the features of TGA are in keeping with a migrainous pathogenesis: the area of putative ischaemia is likely to be in the posterior circulation and migraine has a predilection for the posterior circulation vessels; precipitants, frequently cited as provoking TGA, are known to bring on migraine in susceptible individuals; and TGA is a benign condition like migraine.

Experimental support for the migraine/TGA connection comes from the work of Crowell *et al.* (1984) who measured regional cerebral blood flow using a xenon 133 inhalation technique in 7 patients between 24 h and 14 days postattack; 5 showed either impaired vasomotor response in the boundary zone between the middle cerebral artery and posterior cerebral artery territories, or focal ischaemia. These abnormalities differed from those seen in patients with carotid or vertebrobasilar TIAs and were similar to those found in migraine. Cerebral blood flow (CBF) changes are well documented in migraine (e.g., Norris *et al.*, 1975; Lauritzen *et al.*, 1983). The most consistent abnormality is reduced CBF, particularly in the posterior part of the brain during neurological accompaniments of classical migraine. Direct evidence for vasoconstriction is, however, lacking and it is still uncertain whether the reduced CBF reflects ischaemia secondary to vasospasm or whether it represents decreased metabolism with a secondary reduction in flow (Oleson *et al.*, 1981; Lauritzen *et al.*, 1983).

Recently it has been suggested that the phenomenon of spreading depression (of Leão) may provide a unifying explanation for the CBF abnormalities observed in migraine and for TGA (Olesen and Jørgensen, 1986). Spreading depression can be elicited mechanically, electrically, chemically, thermally, and by sensory stimulation in experimental animals (Bures *et al.*, 1974). It consists of depolarization of neurons, depression of EEG activity and a marked decrease in glucose consumption and CBF. Most of these changes normalize quickly and take place on a narrow zone which spreads at 2–4 mm/min. Behind this wave, CBF remains depressed for 1 h or longer (Lauritzen *et al.*, 1983). Spreading depression can be elicited in the hippocampus (Šramka *et al.*, 1977–1978) and thalamus (Bures *et al.*, 1974). It causes functional ablation and in the hippocampus experimental spreading depression causes amnesia (Bures *et al.*, 1974). It has been suggested that it occurs spontaneously during migraine and accounts for the spreading abnormalities in CBF (Lauritzen *et al.*, 1983). Olesen and Jørgensen (1986) postulated that it may cause TGA, and that it could be precipitated by intense volleys of sensory inputs into the hippocampus, releasing the neurotransmitter glutamate; the latter is a potent cause of spreading depression in animals (Bures *et al.*, 1974). This appealing hypothesis awaits further verification.

It is well recognized that migraine may cause acute confusional states in children (Gascon and Barlow, 1970; Emery, 1977) and occasionally in adults (Feely *et al.*, 1982), but such patients have displayed features of global cerebral impairment rather than a pure amnesia as in TGA. Confusional migraine may be precipitated by minor head trauma (Emery, 1977) and recently an amnesic syndrome triggered by mild covert head injury has been reported in a group of 9 young adults, with the suggestion that it constitutes a variety of traumatic migraine (Haas and Ross, 1986). It could be argued that as migraine is a condition of young adults and TGA a condition of older adults and the elderly it is unlikely that migraine is the cause of TGA. However, migraine may not be as rare in the elderly as is commonly believed (Ziegler *et al.*, 1977). One final strand of evidence to connect migraine and TGA is the fact that headache and/or nausea are not uncommonly reported by patients during or after TGA.

A number of authors have drawn attention to the association between TGA and potential precipitating events such as swimming (especially in cold water), medical procedures and sexual intercourse (Fisher and Adams, 1964; Shuping *et al.*, 1980; Fisher, 1982). In our series, 13% of the prospective cases occurred shortly after a likely precipitating factor and a further 14% reported an emotionally stressful event, of at least moderate severity, in the preceding 24 h. This is not to say that the attacks are hysterical or psychogenic. Observations made on patients during TGA contrast sharply with those made during hysterical fugues (Hodges and Ward, 1989). The role of putative precipitating factors in the pathogenesis of TGA remains unclear. There is need for a controlled study, preferably including TIA patients, although such a study would be clearly very difficult to perform properly.

In conclusion, there is no evidence to support thromboembolic disease as the cause of TGA in the majority of cases. Migraine is associated with TGA and there are a number of good theoretical reasons to implicate migraine in the pathogenesis of TGA. It seems likely that migraine plays a direct causal role in a proportion of cases. Epilepsy may masquerade as TGA and is thus responsible for an important minority of cases. In the remainder of the cases the cause is unclear.

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ADDENDUM

Since the preparation of this paper, a further case-control study of 30 TGA patients has been reported (Guidotti M, Anzalone N, Morabito A, Landi G (1989) A case-control study of transient global amnesia. *Journal of Neurology, Neurosurgery and Psychiatry*, **52**, 320–323).

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QUANTITATIVE ASSESSMENT OF CLASS II MOLECULES IN NORMAL AND PATHOLOGICAL NERVES

IMMUNOCYTOCHEMICAL STUDIES IN VIVO AND IN TISSUE CULTURE

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SUMMARY

We have analysed class II molecules (HLA-DR) expression in human fetal nerves at different stages of gestation, in human control nerves and in nerves of patients with peripheral neuropathies of different aetiology. Immunochemical demonstration of HLA-DR antigens was also performed on isolated human Schwann cells at different times in culture, from the same nerves.

In normal nerves, HLA-DR positive material is localized only on endothelial and perivascular cells and in rare perineurial and endoneurial cells. In fetal nerves, HLA-DR positive material is already present by the sixteenth week of gestation. Quantitative analysis of HLA-DR molecules density in pathological nerves showed a wide heterogeneity in different neuropathies with no correlation between the type of pathology and the intensity and pattern of staining. Cultured human Schwann cells obtained from fetal, normal adult and pathological (vasculitic neuropathy) nerves were HLA-DR positive and the percentage of positive cells increased with time in culture. DR antigen appearance on human Schwann cells may reflect not only an immunologically-mediated phenomenon but also a dependence on axon-Schwann cell interaction.

INTRODUCTION

The immune response-associated class II (Ia or DR) antigens have been found in mononuclear and Schwann cells within the nerves of patients with chronic inflammatory demyelinating polyneuropathy, the Guillain-Barré syndrome, hereditary motor and sensory neuropathy type I and demyelinating neuropathy associated with monoclonal IgM (Cadoni *et al.*, 1986; Pollard *et al.*, 1986, 1987). Since the induction of these molecules on the surface of the cell might enable it to present the antigens to reactive lymphocytes (Hirschberg *et al.*, 1980; Fontana *et al.*, 1984; Fierz *et al.*, 1985), it has been suggested that this expression on myelin-forming cells has important implications for the pathogenesis of the disease (Pollard *et al.*, 1987).

In order to verify the specificity of this phenomenon, we performed a histospectro-

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photometric analysis of DR molecules' optical density on frozen sections of nerves removed at biopsy from patients with neuropathies of different origin. Sections of normal human peripheral nerves at different stages of development were also studied in order to establish whether the appearance of the HLA-DR antigens is a developmentally regulated phenomenon.

In previous studies, unstimulated rat and mouse Schwann cells did not express class II molecules in vitro (Hirsch *et al.*, 1983; Lisak *et al.*, 1983; Bartlett *et al.*, 1984). In addition, human Schwann cells obtained by dissociation of fetal dorsal root ganglia (Kim *et al.*, 1985) and fetal peripheral nerves (Samuel *et al.*, 1987) have been shown to be DR negative. However, oligodendrocytes and astrocytes isolated from adult human brains of patients dying without primary CNS disease have been reported by some (Kim *et al.*, 1985) but not all groups (Lisak *et al.*, 1983) to be DR surface positive. For this reason, we have also studied cultures of human Schwann cells derived from fetal and adult normal and pathological nerves to study the expression of MHC class II as well as class I antigens.

MATERIAL AND METHODS

Patients and tissue samples

Human adult sural nerves were obtained from subjects with no clinically apparent neuropathies undergoing orthopaedic surgical procedures. Sural nerves from 24 patients with well-documented peripheral neuropathy of different type and aetiology (*see* Table 1), followed at the Department of Neurology of the University of Milan, were examined. The diagnosis of peripheral neuropathy was made by clinical and laboratory investigations. Biopsy samples from 2 schwannomas were also studied. Fetal femoral nerves were obtained from 12 therapeutic abortions according to current Italian laws. Samples from 11 to 22 wk fetuses, as determined by crown-rump length (O'Rahilly, 1972) were examined. The nerves were rapidly frozen within 20 min following biopsy procedure by immersion in isopentane cooled with liquid nitrogen and stored at −70° C for immunocytochemistry or fixed in glutaraldehyde for electron microscopy.

Morphological studies on nerve biopsies

Cryostat sections of nerves were stained with haematoxylin and eosin, modified trichrome and Congo red. For teased fibre analysis a specimen of nerve biopsy was fixed in 2.5% glutaraldehyde, postfixed in 2% osmium tetroxide and transferred to glycerol. Morphological abnormalities of teased nerve fibres were classified according to Dyck *et al.* (1984). Morphometric analysis of nerves was performed on semithin sections stained with toluidine blue using the image analyser MOP-AM03.

For electron microscopy, nerves were fixed in glutaraldehyde and osmium ferrocyanide, dehydrated, embedded in Spurr's medium, sectioned, stained with uranyl acetate and lead citrate, and examined with a Zeiss electron microscope.

Monoclonal and polyclonal antibodies

Three different monoclonal antibodies (MAb) to different HLA-DR epitopes were used. The first MAb (IgG_2) reacts with a nonpolymorphic HLA-DR epitope (Becton and Dickinson); the second (IgG_2) reacts with the products of the HLA gene subregion DR and with all the products of the subregions DX and DQ except DQw1 (Dako, Santa Barbara, USA); the third MAb was a kind gift from Dr James Hoxie (University of Pennsylvania). The specificity of this MAb has not yet been completely determined. Two different MAb to human macrophages (Dako, BDM 11, code M 718, IgG_1) and to macrophages-monocytes (Leu M3 or Mo2, Becton and Dickinson, Erembodegen, Belgium, IgG_{2b}) were used. MAb anti-Leu 7 (IgM), a marker for myelin (Schuller-Petrovic *et al.*, 1983), was purchased from Becton and Dickinson. Anti-HLA-ABC (nonpolymorphic MHC Class I) MAb (IgG_{2a}), anti-C_3b receptor (C_3bR) MAb (IgG_1) and anti-Interleukin 2 receptor (IL2-R) MAb (IgG_1) were purchased from Dako. An anti-schistosome MAb (IgG_1) was used as a nonspecific control. Rabbit antiserum to bovine S100 protein (Dako), was used as a marker for mature Schwann cells (Scarpini *et al.*, 1986) and normal rabbit serum served as a control.

Immunoperoxidase and immunofluorescence staining of nerve sections (Table 1)

Cross and longitudinal serial cryostat sections (5 μm) were cut, fixed in cold methanol for 1 min, and washed in 0.5 M Tris, pH 7.4, with 1% fetal bovine serum. Sections were incubated overnight at 4° C with anti-DR MAb (Becton and Dickinson) and then with biotinylated antimouse antibody (1:75) (Vector Laboratories, Burlingame, CA) for 30 min and with avidin-biotinylated peroxidase complex (Vector) for 45 min. Washes (10 min) in 0.5 M Tris, 1% fetal calf serum (FCS) were performed between each step. After the last wash, aminoethylcarbazole (Dako) was applied for 15 min. Sections were rinsed in water, counterstained with Mayer's haematoxylin, mounted in glycerin, and examined by light microscopy.

Staining of serial cross-sections with other MAbs (at optimal concentration) was performed applying the same techniques.

TABLE 1. SUMMARY OF ANTIBODIES AND TECHNIQUES EMPLOYED IN NERVE SECTIONS AND TISSUE CULTURE

	Immunoperoxidase and immunofluorescence		
	Nerve sections		*Schwann cells cultures*
Antibody	*Peroxidase*	*IF*	*IF*
HLA-DR	+*	+	+
HLA-ABC	+	+	+
C3bR	O	O	+
IL-2R	O	O	+
Schistosome	+	+	+
Leu M3, Mo2	+	+	+
EBM 11	+	+	+
Leu 7	+	+	+
S100 protein	+	+	+
NRS	+	+	+

+ = tested; O = not tested; IF = indirect immunofluorescence; * = with quantitative peroxidase; NRS = normal rabbit serum.

Densitometric quantitation was made after anti-HLA-DR and control serum staining with immunoperoxidase. Measurements of the relative adsorbance of the aminoethylcarbazole stain after the reaction for HLA-DR was made using a Leitz Zonax histospectrophotometer (Bresolin *et al.*, 1987). Fifty scans were obtained at ×100 with a 3.2 mm diaphragm on separate uncounterstained slides for normal and patient specimens. The adsorbance was expressed as a percentage of the reduction of the light passing through the section after immunocytochemical reaction. The mean ±SD adsorbance value of 50 scans on each nerve section was calculated on an Epson HX-20 computer.

For immunofluorescence staining of nerve sections an indirect procedure was used. Sections (5 μm) were fixed in cold methanol for 1 min and washed in 0.1 M phosphate-buffered saline (PBS), pH 7.6, with 1% (v/v) fetal bovine serum. They were then incubated overnight at 4° C with the first antibody (at optimal concentration), washed in PBS for 20 min and then incubated with fluorescein isothiocyanate-conjugated goat antimouse immunoglobulin (KPL) at a 1:40 dilution.

For immunofluorescence staining with anti-S100 protein antiserum, sections were first incubated with anti-S100 antiserum (1:200), then with fluorescein isothiocyanate-conjugated goat antirabbit immunoglobulin (KPL) at a 1:40 dilution.

Tissue culture

Human fetal Schwann cells were cultured as previously reported (Scarpini *et al.*, 1988). Briefly, nerves obtained from 4 fetuses (1 17 wk, 1 18 wk, 2 19 wk) were removed aseptically and put in ice-cold Ca_2- Mg_2-free Dulbecco's PBS (GIBCO). They were cleaned of epineural connective tissue under a dissecting microscope and transferred in PBS containing 0.37% (w/v) trypsin (GIBCO, 043-5090-H, 2.5% solution) and 0.03% (w/v) collagenase (Sigma C-0255; 800 U/mg). After mincing with scissors, they were incubated in the enzyme solution for 45−60 min at 37° C. The culture was resuspended with a Pasteur pipette 20 times, centrifuged at room temperature and the pellet washed 3 times (2000 rpm for 3 min) with growth medium (Minimal Essential Medium (MEM) with Earle's salts, GIBCO) containing 20% (v/v) FCS, 600 mg/100 ml glucose and antibiotics. The cells were resuspended in 2 ml of medium, counted and seeded at a density of 50 000 cells/ml on glass coverslips which were maintained in 24 multiwell plates (Falcon).

Schwann cells from human adult nerves were obtained from 2 patients without neuropathy (Cases 2, 4) undergoing orthopaedic surgical procedures and from 2 patients with vasculitic neuropathy (Cases 9, 12). Nerves were removed using sterile techniques and put into Dulbecco's PBS without calcium and magnesium and with antibiotics and fungizone. The epineurium was carefully removed under a dissecting microscope and discarded. The remaining nerves were minced with scalpels, centrifuged and transferred to growth medium containing 15% (v/v) FCS, 25 mM HEPES, 1.25 units dispase (crude, Boehringer 165-859), 0.05% (w/v) collagenase (Worthington 4196), 0.1% (w/v) hyaluronidase (Sigma H-3884). The growth medium was MEM with Earle's salts (GIBCO) containing 15% FCS, 600 mg/100 ml glucose and antibiotics (75 units/ml penicillin, 75 mg/ml streptomycin and 0.025 mg/ml amphotericin B). The culture was resuspended with a Pasteur pipette and incubated overnight at 37° C in 5% CO_2, 95% air. The next day the tissue was centrifuged for 5 min at 1500 rpm, the medium was removed and replaced with growth medium without serum, containing 1.25 units/ml dispase and 0.05% collagenase. After 45 min of incubation at 37° C, it was again resuspended, centrifuged, and the pellet washed 3 times with growth medium containing 15% (v/v) FCS, antibiotics and fungizone. The cells were seeded onto glass coverslips which were maintained in 24 multiwell plates. The plated suspension contained a few round cells and many individual nerve fibres and myelin fragments, presumably with attached Schwann cells. Coverslips were left for 48 h in the incubator before adding fresh medium. Immunostaining of cells was performed after 1, 2 and 3 wks in culture. Some cultures were kept in serum-free medium 2−6 days before immunostaining.

All cultures were routinely fed 3 times weekly and were kept at 37° C in an atmosphere of 5% CO_2 and air. They were observed daily and photographed periodically under phase contrast microscopy.

Immunofluorescence staining of cultured cells

After 1, 2 and 3 wks in culture, cells were incubated with anti-HLA-DR MAb diluted 1:10, washed 5 times with MEM, overlaid with rhodamine-conjugated goat antimouse immunoglobulin, washed 5 times with MEM, fixed with ice-cold 5% acetic acid (v/v) in ethanol, washed 5 times with MEM, and rinsed once with water. The coverslips, mounted in glycerol/PBS (1/1, v/v) were observed using a Zeiss microscope fitted for epifluorescence. For double labelling, some cultures were stained with the HLA-DR MAb, followed by incubation with tetramethyl rhodamine isothiocyanate-conjugated goat antimouse immunoglobulin. The cultures were then fixed in 3% formaldehyde for 5 min at 0−4° C, treated with 0.005% Nonidet P-40 for 10 min, incubated with anti S100 antibody and with fluorescein isothiocyanate-conjugated goat antirabbit immunoglobulin. The same procedure was used for staining with anti-HLA-ABC, anti-C_3bR, anti-IL2-R and antischistosome antibodies, all used at 1:20 dilution. The 3 anti-HLA-DR MAbs were compared in the first experiments of normal and pathological nerves. The percentage of positive cells was equivalent for all of them and therefore the MAb from Becton and Dickinson was used for all the following experiments.

RESULTS

DR antigen expression in nerve sections

Normal nerves. As mentioned, the three different anti-HLA-DR MAb showed no differences in staining pattern and intensity. In normal adult nerves, DR-positive staining

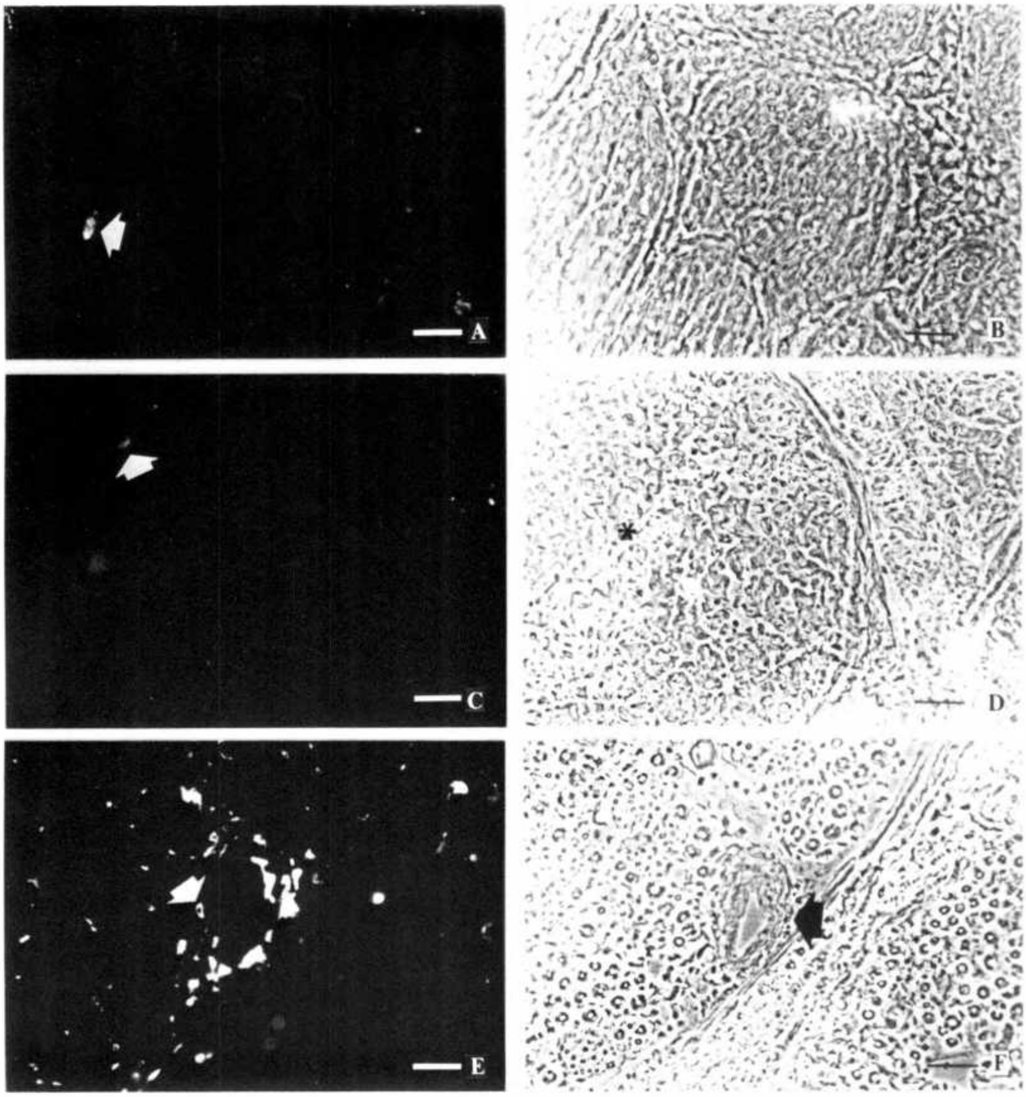

FIG. 1. Anti-HLA-DR immunofluorescence (A, C, E) and phase-contrast (B, D, F) microscopy of human nerves. A, B, 16 wks of gestation; C, D, 20 wks; E, F, normal adult nerve. Nerve at 20 wks displays birefringent myelin rings (*). HLA-DR positive material, present sparsely within the nerve fascicles of all samples, is indicated by arrows in A and C. Note positivity of some mononuclear cells (E, arrow) around an endoneurial vessel (F, arrow) in the adult nerve. Bars = 50 μm.

always occurred only on endothelial and perivascular cells of endoneurial capillaries and in occasional perineurial and endoneurial cells (figs 1E, F; 2A, D). Fetal nerves at different stages of development showed a similar pattern (fig. 1A, B, C, D). Schwann cells, identified by anti-S100 antibody binding in adjacent sections (fig. 2C, D), appeared HLA-DR negative. Densitometric measurement of adsorbance of the reaction with immunoperoxidase in normal nerves showed an average value of 8.782% ±1.65.

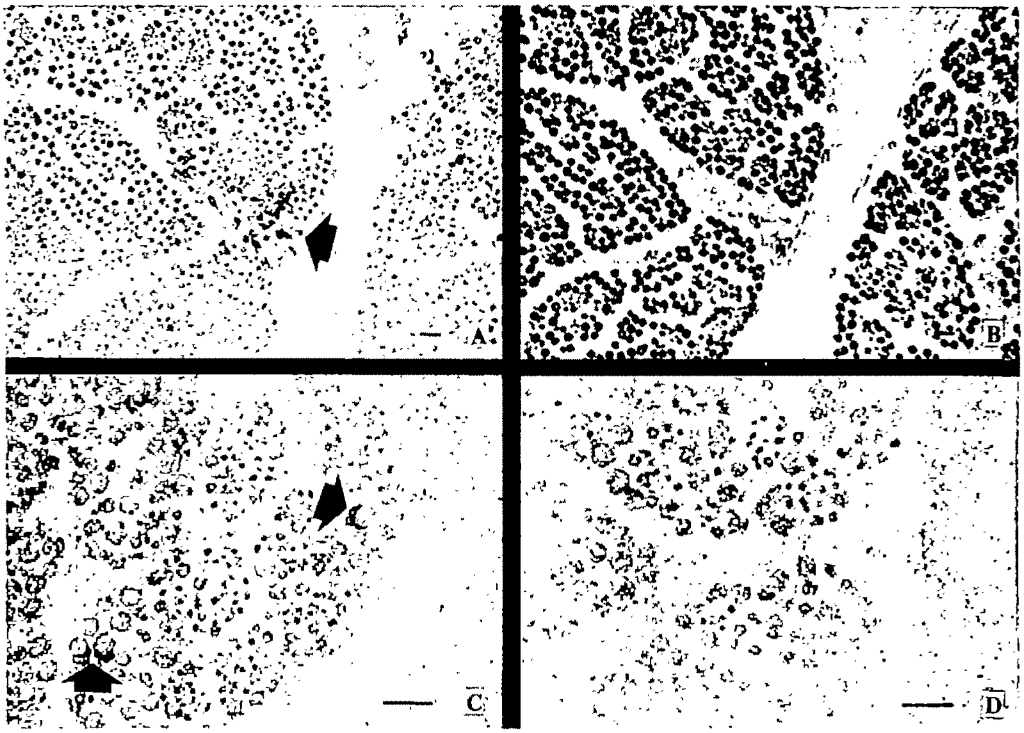

FIG. 2. Immunoperoxidase staining of section of a normal adult nerve, counterstained with Mayer's haematoxylin. Immunoperoxidase staining allows a better localization of the reaction product. HLA-DR positive cells are seen around vessels (A, arrow) and endothelial cells are also reactive. The degree of myelination can be determined on serial cross-sections by staining with anti-Leu 7 antibody (B). Schwann cells can be identified on frozen sections by anti-S100 protein antibody (C, arrows). DR-positive cells never present this peculiar pattern of staining. Note that in D (cross-section adjacent to A and B stained with anti-S100), no positive cells are present. Bars = 50 μm.

Immunofluorescence and immunoperoxidase staining with MAb antimacrophage and with Mo2 MAb only rarely was present within normal adult and fetal nerves.

Pathological nerves. In most pathological nerves, dense staining for DR antigen was found within the endoneurium and perineurium and on endothelial cells (fig. 3). The pattern of staining was qualitatively similar to that of the control nerves, but greater in amount. HLA-DR positive material was more widely seen in the endoneurium and a larger number of perineurial and perivascular HLA-DR positive cells were detectable.

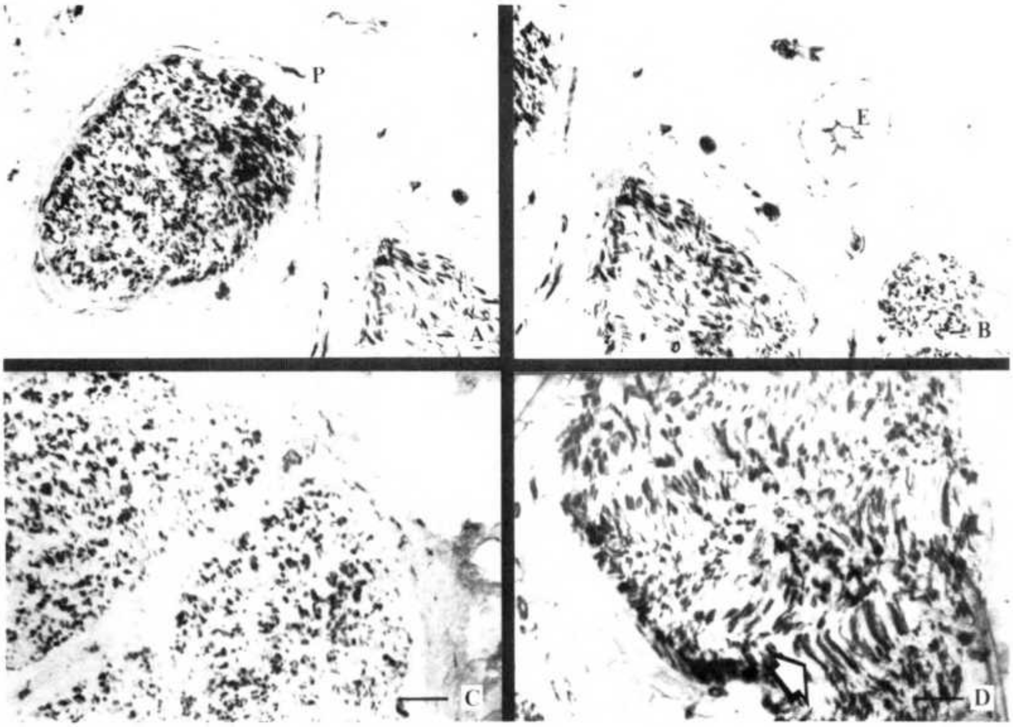

FIG. 3. Transverse section of the sural nerve from 2 patients with vasculitic neuropathy (*Case 9*, A, B; *Case 11*, C) and from a patient with a neuropathy of unknown origin (*Case 23*, D). Immunostaining with mouse monoclonal antibody to human HLA-DR. Note dense reaction product within nerve fascicle, perineurial cells (P, A) and endothelium (E, B). Very dense expression of class II molecules corresponds to a high value of adsorbance (*Case 9*: 36.6%; *Case 23*: 31.9%; *Case 11*: 42.9%). On longitudinal areas (D) the typical linear pattern of the myelin/Schwann cell plasmalemma is evident (arrow). Bars = 50 μm.

The density of staining varied in different nerves. The values of adsorbance for each nerve are listed in Table 2. In fig. 4 these values are grouped according to the pattern of nerve pathology. Some nerves with a marked reduction of myelinated fibre density (Cases 5, 15, 16), with (Cases 5, 16) or without (Case 21) axonal degeneration showed an adsorbance value comparable with normal controls. In other cases (9, 11, 23), a strong increase of DR density was present, with the typical linear pattern of the myelin sheath/Schwann cell plasmalemma in longitudinal areas (fig. 3D, arrow). No correlation (Draper and Smith, 1981) between mean HLA-DR adsorbance of the nerve section and fibre density was observed (R 0.351).

In the nerve of a patient with occasional onion-bulb formations (Case 5) the staining was present in concentric arrangements of Schwann cell lamellae around the central axon (Fig. 5B, arrows). Likewise, in the nerve of the patient with thickened myelin sheaths around some fibres (Case 10), the outer myelin ring was clearly strongly positive (fig. 5A, arrows).

In all the nerves with axonal neuropathy and strong DR staining, the number of

TABLE 2. HLA-DR STAINING DENSITY RELATED TO CLINICAL AND PATHOLOGICAL FEATURES OF THE NEUROPATHIES

						*Teased fibre appearances**			
Case	*Age (yrs)*	*Disease*	*Duration*	*Myelinated fibre density (per mm^2)*	*Pathology*	*Normal appearance*	*Axonal degeneration*	*Demyelination and remyelination*	*HLA-DR ± SD***
1	28	Normal	–	6490	Control	***	***	***	8.670 ± 1.85
2	60	Normal	–	6955	Control	***	***	***	7.878 ± 1.63
3	18	Normal	–	7423	Control	***	***	***	9.757 ± 1.15
4	21	Normal	–	6781	Control	***	***	***	8.823 ± 1.94
5	52	HMSN II	30 yrs	775	Axonal	48	14	38	9.571 ± 2.14
6	23	HMSN II	4 yrs	5250	Axonal	77	5	17	14.160 ± 1.48
7	64	Vasculitic n	3 mos	1000	Axonal	14	78	8	12.703 ± 2.06
8	44	Vasculitic n	2 yrs	2725	Axonal	71	5	24	11.293 ± 3.80
9	55	Vasculitic n	5 mos	1437	Axonal	31	67	2	36.300 ± 5.50
10	40	Vasculitic n	6 yrs	2175	Demyel.	70	0	30	29.877 ± 8.42
11	54	Vasculitic n	2 mos	3621	n.d.	n.d.	n.d.	n.d.	33.883 ± 7.57
12	41	Vasculitic n	7 yrs	1658	n.d.	n.d.	n.d.	n.d.	9.967 ± 2.15
13	49	CIDP	6 yrs	1212	Demyel.	62.4	1.6	36	14.343 ± 1.64
14	40	Motor neuropathy	6 mos	2500	Mixed	88	1	11	18.880 ± 3.29
15	37	MERRF+n	4 yrs	675	Normal	92.3	1.4	7.3	9.900 ± 2.53
16	73	Eosinophilic n	2.5 yrs	812	Axonal	n.d.	n.d.	n.d.	9.925 ± 2.47
17	27	Porphyric n	2.5 yrs	2737	Normal	98.5	1.5	0	11.647 ± 2.15
18	68	Ischaemic n	4 mos	3475	Mixed/axonal	73	6	21	21.053 ± 4.57
19	40	Unknown aetiology	5 yrs	3150	Mixed	81	1	18	24.670 ± 6.07
20	38	Unknown aetiology	8 yrs	1862	Mixed/axonal	81	3	16	18.350 ± 1.72
21	45	Unknown aetiology	2 yrs	5425	Normal	99	0	1	8.033 ± 2.17
22	23	Unknown aetiology	3 yrs	3975	Normal	95	1	4	7.897 ± 2.15
23	56	Unknown aetiology	2 yrs	1800	Axonal	85	15	0	42.887 ± 4.99
24	43	Nutritional n	6 mos	600	Axonal	69	28	3	26.790 ± 3.78
25	73	Diabetes	10 yrs	695	n.d.	n.d.	n.d.	n.d.	22.750 ± 3.50
26	62	Diabetes	10 yrs	3497	n.d.	n.d.	n.d.	n.d.	15.427 ± 1.54
27	62	Diabetes	6 yrs	2953	n.d.	n.d.	n.d.	n.d.	20.540 ± 3.11
28	79	Paraneoplastic n	1 yr	3300	Mixed	80	2	18	26.830 ± 5.02

* Teased fibres were classified according to Dyck *et al.* (1984), and expressed as a percentage. ** The number expresses the average value ± SD of densitometric measurement of optical density (adsorbance) of HLA-DR immunoreaction on nerve sections. *** According to Ohi *et al.* (1985) normal values are 89 ± 9, 9 ± 9 and 0.5 ± 5, respectively. HMSN = hereditary motor and sensory neuropathy; n.d. = not done; n = neuropathy; demyel. = demyelinating; MERRF = myoclonus epilepsy with ragged red fibres.

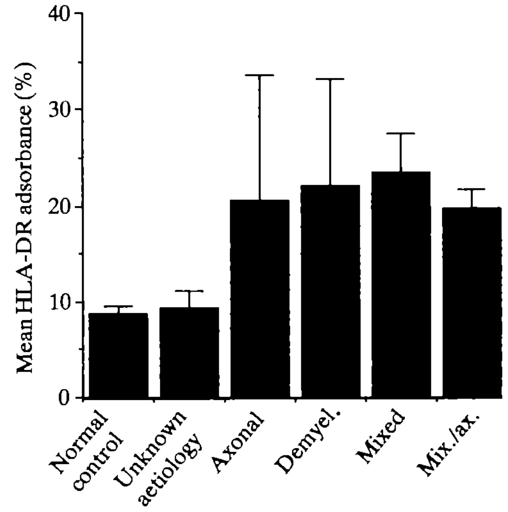

FIG. 4. Quantitative peroxidase and nerve pathology. The intensities of the HLA-DR immunoreaction in different nerves are grouped according to the type of pathology. All the forms present increased adsorbance compared with the normal samples. Unknown = neuropathy of unknown aetiology with undetermined pathology; Demyel. = demyelinating; Mix./ax. = mixed axonal-demyelinating or primarily axonal.

DR-positive cells was higher than that of infiltrative monocyte-macrophages, as judged by anti-Mo2 staining and electron microscopy (Case 11, fig. 6A, B).

Strong differences in DR expression were also seen in nerves from different patients with the same disease. In the nerves with vasculitic neuropathy, class II molecules were expressed with very high density in 3 nerves (Cases 9, 10, 11) reaching a densitometric value of 36.3, 29.9 and 33.9, respectively, and more sparsely in 3 others (Cases 7, 8, 12; densitometric values 12.7, 11.3, 9.97).

In a case of chronic inflammatory demyelinating neuropathy (CIDP, Case 13), in which a nerve biopsy was undertaken immediately after a clinical relapse, only a moderate increase of DR intensity (14.3%) was present (fig. 6C, D).

No correlation (R 0.29) between the duration of the disease before nerve biopsy and the value for the optical density of the DR immunoreaction was observed, even within a relatively homogeneous group of diseases such as neuropathy due to vasculitis. The immunohistochemical analysis of 2 such cases of schwannoma demonstrated the presence of a high number of HLA-DR positive cells, often with a fibrillar pattern in some longitudinal areas (fig. 5C, D). This is in agreement with previous studies (Lisak *et al.*, 1986) demonstrating HLA-DR positive cultured Schwann cells from dissociated neurofibromas.

Immune (vasculitic, CIDP, eosinophilic and paraneoplastic) and nonimmune neuropathies showed no differences in pattern and intensity of HLA-DR staining.

DR antigen expression in cultured human Schwann cells

Elongated bipolar or multipolar cells with oval nuclei (Schwann-like cells), obtained from dissociation of all human adult and fetal nerves showed strong membrane reactivity

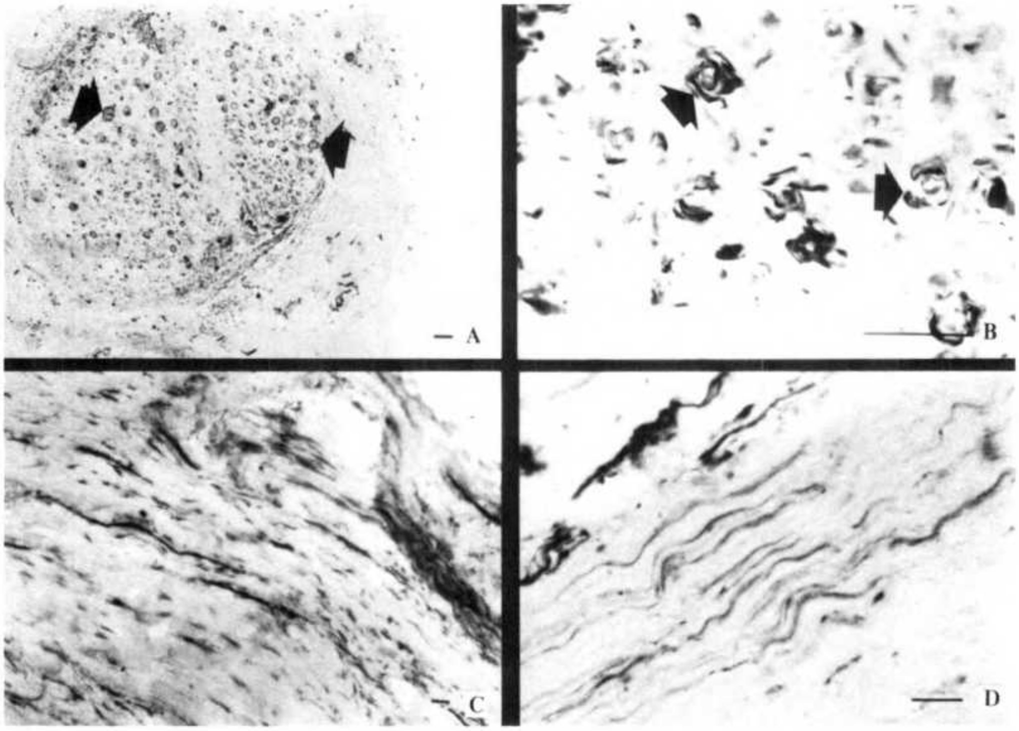

FIG. 5. Immunostaining of sural nerves (A, vasculitic neuropathy, *Case 10*; B, HMSN II, *Case 5*) and of a schwannoma (C, D) with anti-HLA-DR MAb. A, arrows point to some thickened myelin rings. Note reaction product on the external part of the nerve fibre. B, arrows point to well developed 'onion-bulb' formations. The reaction product is localized in concentric arrangements of Schwann cell lamellae around the central axon. C, D, large numbers of HLA-DR positive cells, often with a fibrillar pattern in longitudinal areas. Bars = 50 μm.

with anti-HLA-DR MAb (fig. 7A, D). The identity of these cells as Schwann cells was verified by double staining with anti-S100 protein serum (fig. 7B, E). The percentage of Schwann cells (S100 protein-positive cells) which were positive for HLA-DR antigen is shown in fig. 8. Since we only studied cultures from a few biopsies we are unable to ascertain if there is an effect of duration of culture.

Both fetal and adult human Schwann cells kept in serum-free medium up to 6 days before staining were HLA-DR positive (fig. 9D) and the percentage was comparable with that of parallel cultures maintained in FCS supplemented medium. Schwann cells from both adult and fetal nerves were also MCH I positive (fig. 10) and negative with anti-C_3bR, anti-IL2-R and antimacrophage antibodies.

DISCUSSION

We have analysed the expression of class II molecules in human fetal nerves, in nerves of patients with peripheral neuropathies of different histological pattern and aetiology,

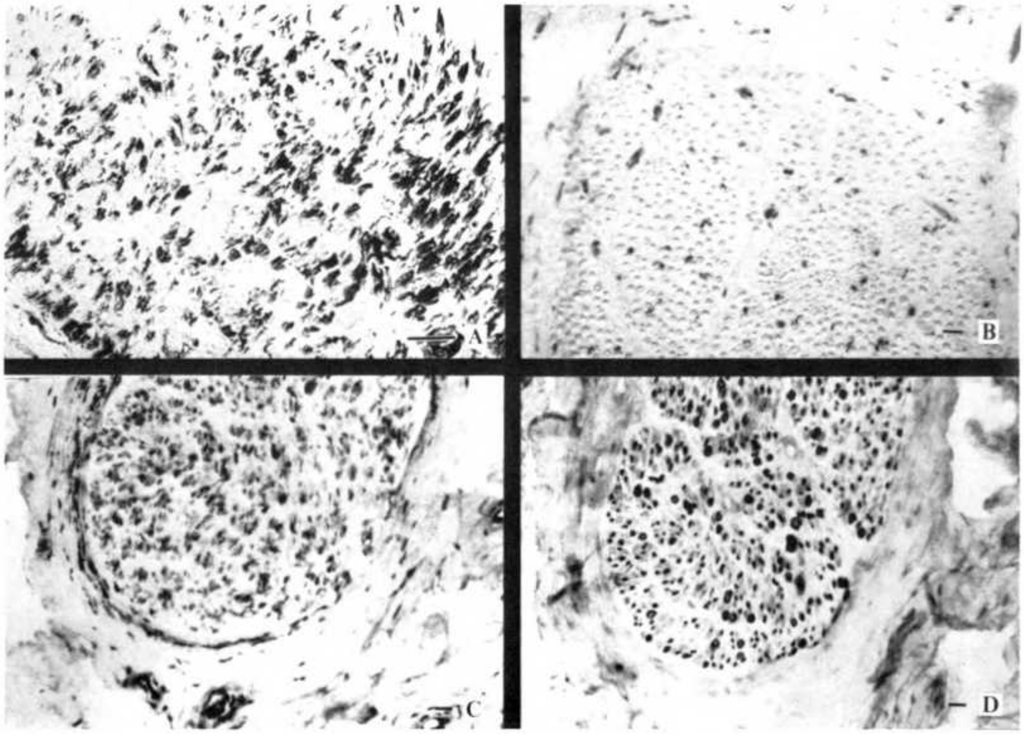

FIG. 6. Transverse sections of sural nerve from *Cases 11* (vasculitis, A, B) and *13* (CIDP, C, D). Immunostaining with anti-HLA-DR MAb (A, C), antimacrophage-monocyte MAb (B) and anti-Leu 7 MAb (D). Comparing A with B, the density of HLA-DR positive cells clearly exceeds the number of macrophages and monocytes. In C only a moderate increase of DR intensity within the fascicle is present (adsorbance 14.4). Adjacent serial section stained with anti-Leu 7 MAb (D) shows the degree of myelination. Bars = 50 μm.

and on human Schwann cells in culture. In the human these molecules are normally found on B lymphocytes, activated T lymphocytes, some cells of the macrophage-monocyte series, dendritic cells, Langerhans cells, thymic epithelial cells, endothelial and some epithelial cells in mammals and on certain tumour cells (Winchester and Kunkel, 1979). In pathological conditions, especially associated with inflammation, HLA-DR antigens have been reported by some groups on cells not generally DR bearing, including astrocytes (Traugott and Raine, 1985). HLA-DR positive material is present on Schwann cells in some pathological conditions (Cadoni *et al.*, 1986; Pollard *et al.*, 1986, 1987; Mancardi *et al.*, 1988). Our studies support these findings, based on the pattern of staining that we observed within hypertrophic nerves where concentric layers of reaction product outline the Schwann cell lamellae. We and others have identified HLA-DR antigens on infiltrating cells, endothelial cells and perineurial cells, as well as in pathological nerves.

Quantitative analysis of HLA-DR molecules density in pathological nerves showed a wide heterogeneity in different neuropathies. Both inflammatory/immunopathological

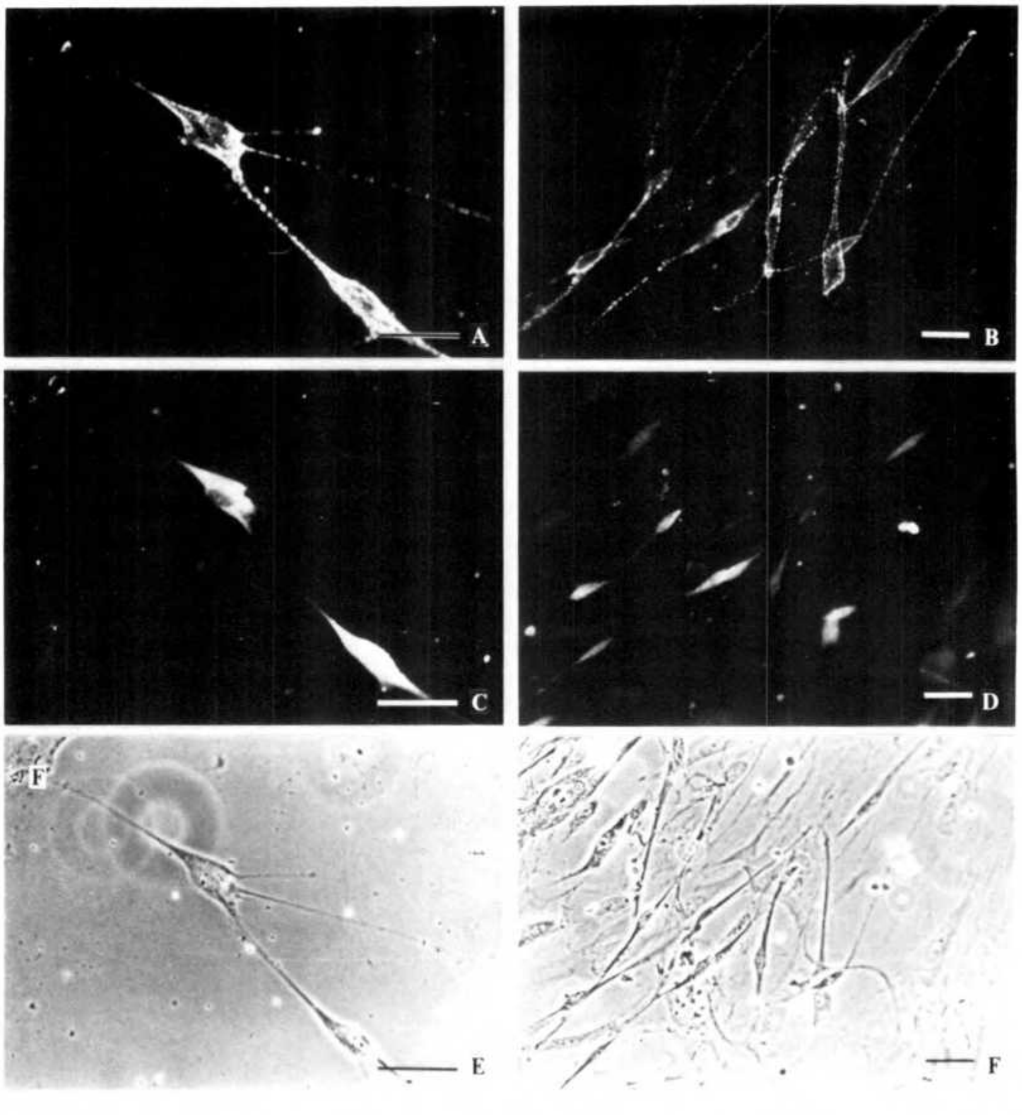

FIG. 7. A, C, E, double labelling of cultured human Schwann cells by monoclonal HLA-DR antibody and rabbit S100 antiserum. Cells were isolated from the sciatic nerve of a 21-yr-old male and cultured for 7 days. Note the DR surface labelling of the S100 positive Schwann cells and the absence of surface labelling on the fibroblast (F) seen under phase contrast in E; 66.7% of S100 positive cells were HLA-DR positive. Bars = 50 μm. B, D, F, Schwann cells from the same subject, cultured for 21 days; 76.6% of S100 positive cells were HLA-DR positive. A, B, HLA-DR-rhodamine immunofluorescence; C, D, S100-FITC immunofluorescence; E, F, phase-contrast microscopy.

and degenerative diseases of the nerve can result in increased HLA-DR immunoreactivity. Neither the duration of the disease, the type of pathology of the nerve nor the myelinated fibre density can be correlated with the staining intensity and distribution. It would seem likely that both the amount and distribution of HLA-DR is influenced by several, as

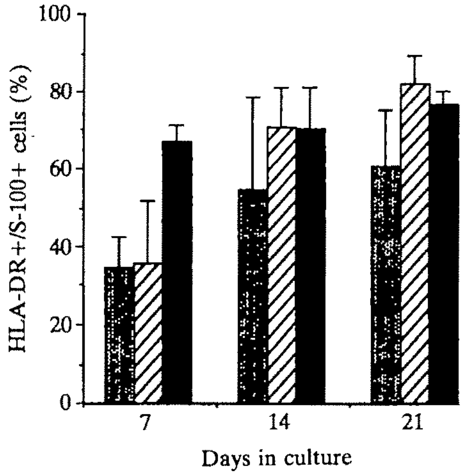

FIG. 7. A, C, E, double labelling of cultured human Schwann cells by monoclonal HLA-DR antibody and rabbit S100 antiserum. Cells were isolated from the sciatic nerve of a 21-yr-old male and cultured for 7 days. Note the DR surface labelling of the S100 positive Schwann cells and the absence of surface labelling on the fibroblast (F) seen under phase contrast in E; 66.7% of S100 positive cells were HLA-DR positive. Bars = 50 μm. B, D, F, Schwann cells from the same subject, cultured for 21 days; 76.6% of S100 positive cells were HLA-DR positive. A, B, HLA-DR-rhodamine immunofluorescence; C, D, S100-FITC immunofluorescence; E, F, phase-contrast microscopy.

yet uncharacterized, factors in addition to the well-recognized effect of gamma-interferon (γIFN).

Dissociated human Schwann cells obtained from fetal and adult nerves were studied at different times in culture with anti HLA-DR MAb. Some cultures were grown without FCS in the medium in order to avoid the possibility of antigenic induction due to agents such as γIFN which can be present in the serum. Cells were identified by two-colour immunofluorescence with anti S100 protein antibody. Cultures obtained from both fetal and adult nerves contained HLA-DR positive Schwann cells. The percentage of positive cells markedly varied as a function of time and no differences were found between cultures grown in the presence or absence of serum. No correlation was observed between the staining intensity and patterns in sections and the number of HLA-DR positive Schwann cells in tissue culture from the same nerves.

Our findings are contrary to previously published studies which demonstrated the failure of detecting DR reaction on cultured human fetal Schwann cells (Kim *et al.*, 1985; Samuel *et al.*, 1987) and on rat and mouse Schwann cells (Lisak *et al.*, 1983; Bartlett *et al.*, 1984; Wekerle *et al.*, 1986) without stimulation with γIFN. From our data, it is clear that human Schwann cells from both fetal and adult nerves are capable of expressing DR and MHC I antigens in the absence of any apparent source of γIFN. More recently, Yong *et al.* (1988) have reported in abstract form the presence of both MHC I and II on fetal human Schwann cells, in agreement with our data on fetal cells presented here.

A possible explanation for differing results in fetal Schwann cells can be that DR molecule presentation on the surface of the cell depends on the method employed. There

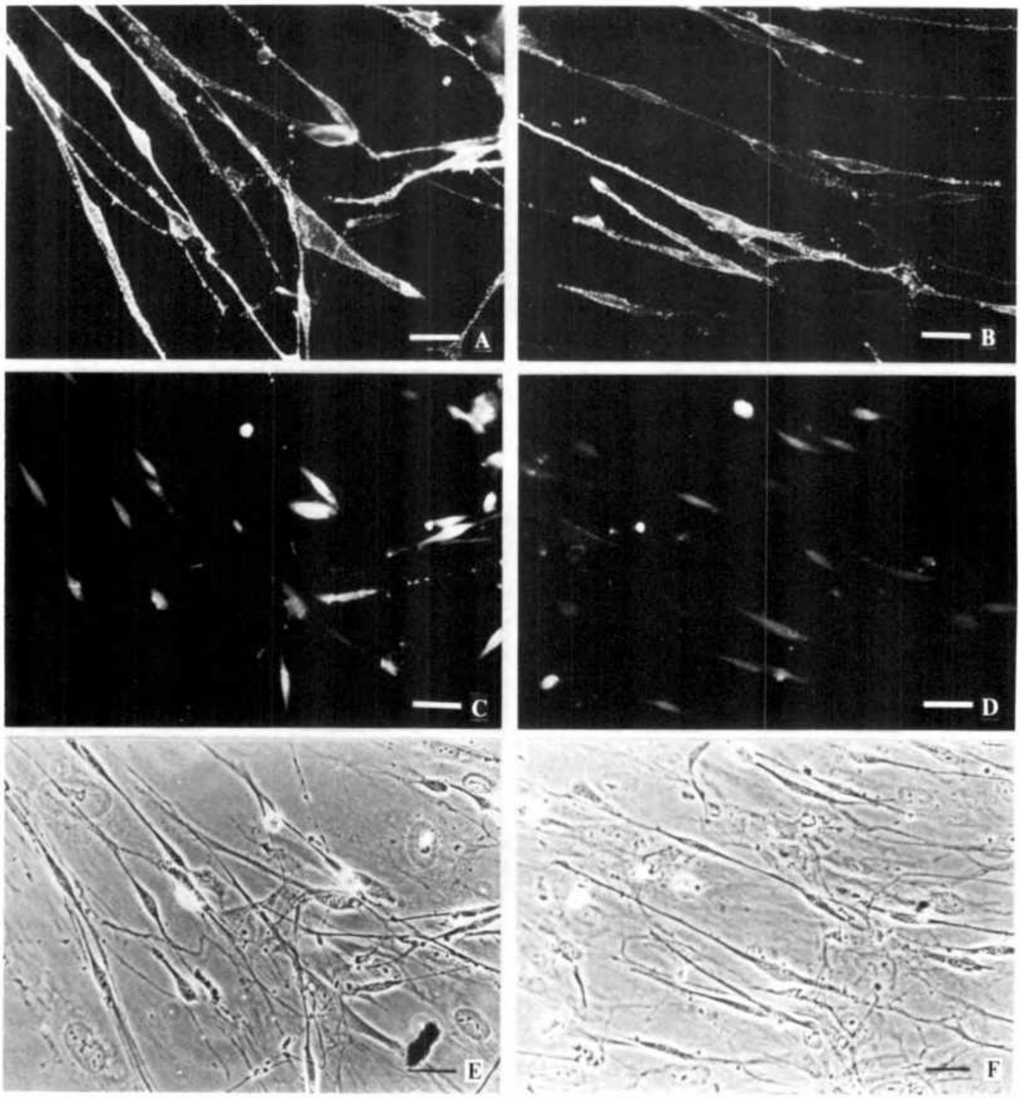

FIG. 9. A, C, E, double labelling of cultured human Schwann cells immunostained as in fig. 8. Cells were obtained from a fetal nerve at 18 wks gestation; 81.8% of the S100 positive cells showed HLA-DR membrane staining after 21 days in culture. B, D, F, parallel cultures grown in the absence of fetal calf serum. Note the identical pattern of HLA-DR staining. The percentage of positive cells is approximately as above. A, B, HLA-DR-rhodamine immunofluorescence; C, D, S100-FITC immunofluorescence; E, F, phase-contrast microscopy. Bars = 50 μm.

are differences in techniques used to isolate and culture human fetal Schwann cells and rodent Schwann cells in comparison with our studies. Among these are longer incubation with trypsin and collagenase (Samuel *et al.*, 1987), inclusion of nerve growth factors (Kim *et al.*, 1985) and the use of dorsal root ganglia (Kim *et al.*, 1985). In any case, only with in situ hybridization with mRNA probes will it be possible to identify

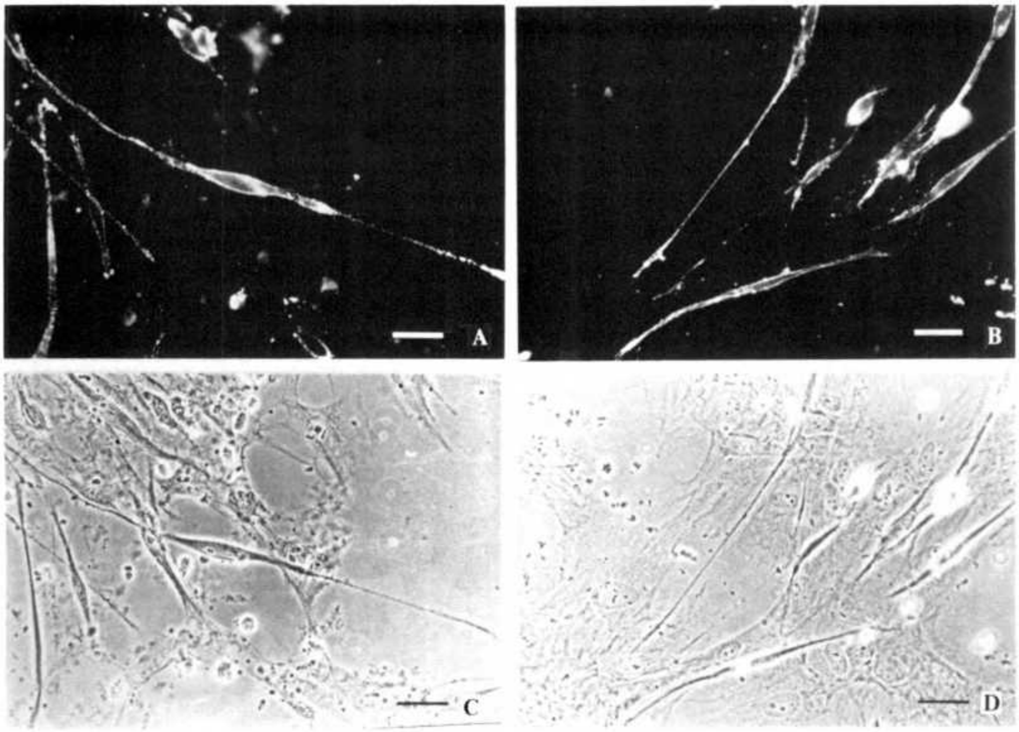

FIG. 10. Human Schwann cells in culture stained with anti-MHC I antibody. Both adult (A, C) and fetal (B, D) cells are clearly surface positive. Bars = 50 μm.

unequivocally HLA-DR producing cells and cells which take this material from the environment.

The presence of HLA-DR on Schwann cells and infiltratory cells in some peripheral neuropathies can easily be explained. It is more difficult to understand why HLA-DR is strongly increased on many cell types in nerve, including Schwann cells, in neuropathies with no signs of inflammation such as type II HMSN, or is expressed in nerves during the fetal stage and on Schwann cell membrane in tissue culture. These findings seem to confirm the hypothesis of Pollard *et al*. (1986), who suggested that class II molecules can be expressed at a certain stage of Schwann cell differentiation or dedifferentiation. In this case, HLA-DR antigen appearance on human Schwann cells may reflect not only an immunologically-mediated phenomenon but also a dependence on axon-Schwann cell interaction.

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MONOCLONAL ANTIBODIES AGAINST SENSORY NEURON SPECIFIC ANTIGENS DEFINE THE EXTENT OF NEURONAL ABNORMALITY IN THE *mf* MUTANT RAT

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SUMMARY

The mutant rat *mutilated foot* (*mf*) is affected by a sensory neuropathy which does not involve the parts of the body innervated by the thoracic cord. The possibility that sensory cells subserving clinically normal regions may be functionally spared by the mutation has been investigated by studying the expression of cell surface oligosaccharides by dorsal root ganglia (DRG) and their central processes in the spinal cord. The study included 3 lactoseries epitopes (TC6, LD2 and LA4) and the globoseries epitope SSEA3. The results show that at cervical and lumbar levels in *mf* rats there are reduced numbers of DRG cells reacting with the various antibodies and less immunostaining in the dorsal horns. The unexpected finding that thoracic ganglia and cord share similar appearances suggests that, in spite of being normal in number and able to produce normal amounts of substance P, thoracic DRG cells in *mf* rats take part in the mutation as shown by their inability to produce normal amounts of oligosaccharides and to transport them to the axon terminals.

INTRODUCTION

Primary sensory neurons in the dorsal root ganglia (DRG) are the first relay neurons mediating the transmission of somatic sensory information from the periphery to the brain. DRG neurons can be subdivided into two main morphological types on the basis of light (Hatai, 1902; Andres, 1961) and electron microscopic (Yamadori, 1970; Lawson *et al.*, 1974; Duce and Keen, 1977) features. More recently, further subdivisions of sensory cells have been proposed on the basis of the localization of neurotransmitters and of the expression of cell surface oligosaccharide antigens (*see* Jessell and Dodd, 1986), both of which are present in the cell bodies and central terminals of primary afferent fibres in the spinal cord.

Degeneration of DRG and autonomic ganglion cells in man underlies a variety of hereditary sensory neuropathies. There are various subtypes of sensory neuropathy (Dyck and Ohta, 1975) each of which has in common the selective involvement of sensory and autonomic functions. Individual neuropathies, however, differ in the time of presentation, mode of inheritance and the sensory modalities which are predominantly

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affected. Hereditary sensory neuropathies have also been reported in the dog (Cummings *et al.*, 1981; Duncan *et al.*, 1982), mouse (Duchen, 1975; Duchen and Scaravilli, 1977*a*, *b*) and rat (Jacobs *et al.*, 1981).

A puzzling feature, present in a number of patients with sensory neuropathies, is the preservation of the sensory modalities at some, usually thoracic, levels (England and Denny-Brown, 1952; Ogden *et al.*, 1959; Campbell, 1970). Normal thoracic sensation has also been observed in the mutilated foot (*mf*) rat (Chimelli and Scaravilli, 1986), a mutant that resembles human hereditary sensory neuropathies (Jacobs *et al.*, 1981). The possibility that morphologically normal sensory cells subserving regions of the body without clinical abnormalities may be also functionally spared by the genetic abnormality in the *mf* rat has been investigated in the present study by examining the expression of cell surface oligosaccharides (*see* Jessell and Dodd, 1986) by the sensory cells in the DRG and by the central processes of the neurons located in the dorsal horn in the spinal cord in normal and *mf* rats.

MATERIAL AND METHODS

Animals

Six mutilated foot (*mf*) and 6 normal Sprague-Dawley 4–6 month old rats of both sexes were used.

Immunocytochemistry

Rats were anaesthetized with pentobarbitone and perfused with 50 ml cold saline followed by 700 ml cold 1.25% glutaraldehyde and 1% paraformaldehyde in 0.1 M phosphate buffer at pH 7.2–7.4. The segments of spinal cord C6–8, T6–8 and L4–5 and the corresponding DRG were dissected out and stored for 4 h in cold fixative before being kept overnight in 10% sucrose. Thick (40 μm) frozen sections of spinal cord and of whole DRG were cut and floated out into phosphate-buffered saline (PBS) pH 7.4. Sections were subsequently incubated for 72 h at 4° C with the monoclonal antibodies (MAbs) SSEA3 (ascitic fluid, Dodd *et al.*, 1984), TC6, LD2 and LA4 (tissue culture supernatant, Dodd and Jessell, 1985) diluted 1:100 in PBS and containing 0.02% Triton X-100. The sections were then washed 4 times in PBS for 1 h and incubated in goat antimouse IgM/peroxidase conjugated serum diluted 1:50 in PBS and containing 0.02% Triton X-100. After overnight incubation, sections were washed twice in PBS for 30 min and in Tris-HCl buffer pH 7.6 for 5 min and incubated for 10 min at room temperature in DAB solution to which 0.01% solution of hydrogen peroxide was added. Finally, the sections were washed 4 times in Tris-HCl pH 7.6, left overnight at 4° C in the final change and mounted onto 'fixed-gel' slides where they were allowed to dry before being mounted in Ralmount.

Quantitative studies

The intensity of immunostaining obtained with the various MAbs varied from light to strong (*see* below). All cells showing a strong reaction and, of those with a weaker staining, only those which included the nucleus were used for morphometric studies.

Cell counts. Total numbers of immunostained DRG cells were counted in serial frozen sections viewed with a ×40 objective. The sign test was used to compare the cell counts in matched pairs of DRG from mutant and control rats according to antibody used and spinal level.

Cell diameters. Cell areas were measured on all chosen profiles using an image analyser (MOP-AM-03 Kontron) linked to an RML 380Z computer. The computer was programmed to calculate the cell diameters assuming circularity of the cross-sectional profiles and to group the diameters at 5 μm intervals.

RESULTS

Expression of antigens in DRG

In normal rats, cells reacting with MAb TC6 were present as isolated cells or in small clusters. While most cells showed homogeneously dark cytoplasm (fig. 1A), in a small number of perikarya the immunolabelling appeared granular, more strongly around the nucleus. On occasion, labelled axons, some of which were seen to emerge from nerve cells (fig. 1A), formed small bundles or a delicate network. No differences were observed at the various levels examined. In *mf* rats, the appearances of the positively stained cells and the intracellular distribution of the immunoreaction were similar to those observed in normal rats (fig. 1B).

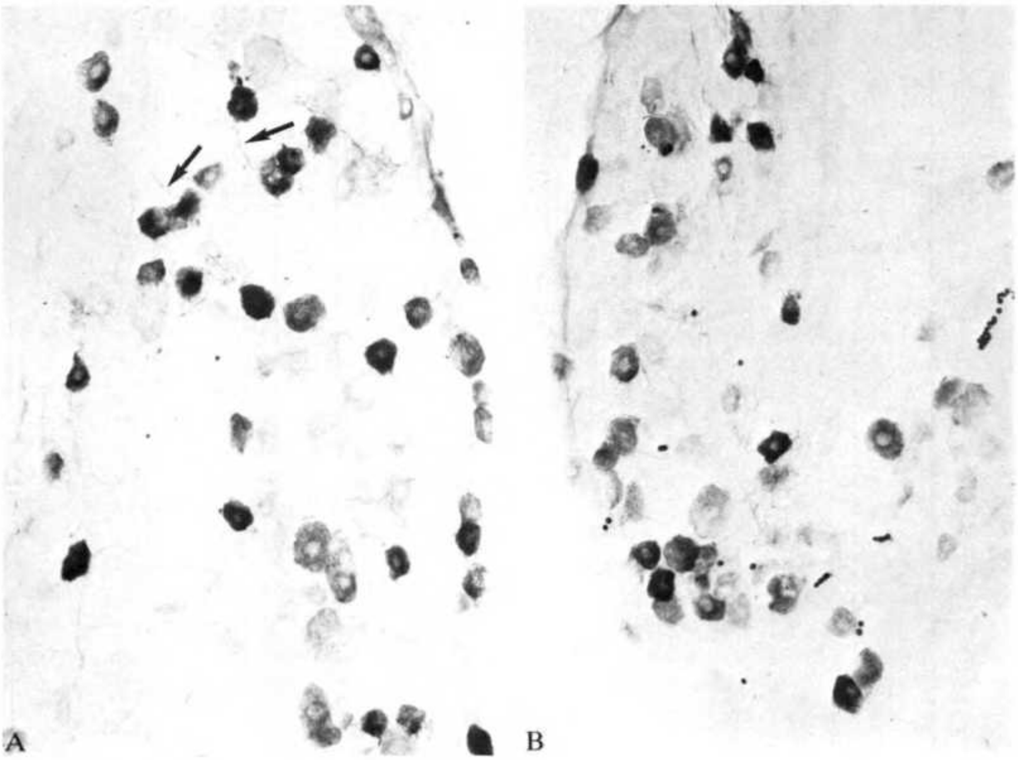

FIG. 1. Photomicrographs of lumbar DRG of normal (A) and *mf* (B) rats incubated with MAb TC6. In both ganglia, cells of different sizes show various degrees of immunostaining. In A, arrows indicate moderately stained axon. × 120.

At all levels examined, the intensity of the immunostaining with MAb LD2 varied from strong to moderate, but only in a few cells did the reaction product completely obliterate the nucleus. A similar pattern was also detected in DRG of *mf* rats.

DRG cells reacting positively with MAb LA4 showed, in all ganglia, a faint staining which was more evident in close proximity to the cell membrane or formed granules resembling Nissl substance. Only on occasion did cells appear heavily stained. Similar features were observed in the ganglia of *mf* rats.

In normal rats, ganglion cells labelled with MAb SSEA3 were scattered and fewer in number than in sections stained with the other antibodies. They formed two distinct groups (fig. 2A). One was made up of large neurons showing variable degrees of immunolabelling, but most of which appeared darkly stained; the other consisted of small cells containing moderately positive material uniformly scattered in the cytoplasm. Cells of intermediate size between the two groups were also seen but were fewer in number. The two groups of cells and their staining properties in the ganglia of *mf* rats were similar to those described in normal animals (fig. 2B).

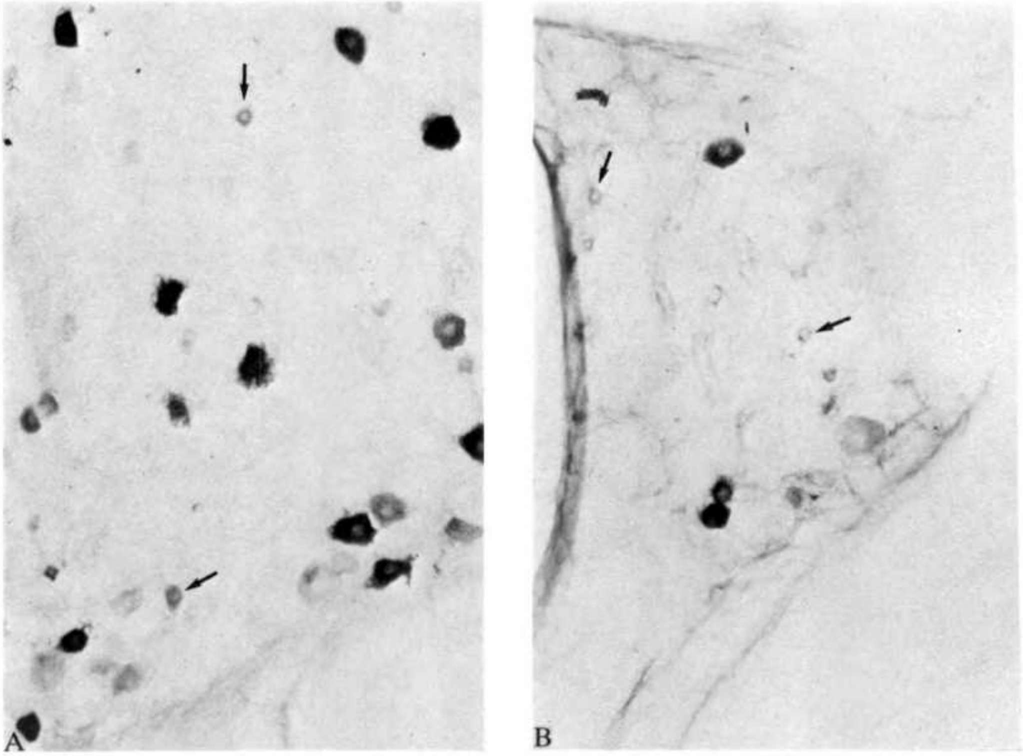

FIG. 2. Photomicrographs of cervical DRG of normal (A) and *mf* (B) rats incubated with MAb SSEA3. Only a small number of ganglion cells in each ganglion immunoreact with this antibody. Arrows indicate ganglion cells of small size. ×120.

Expression of antigens in the spinal cord

The patterns of distribution of MAbs TC6 and LD2 were similar and will be described together. In normal rats a dense band of immunostaining was present in the outer and inner parts of lamina II and, in some specimens, in the tract of Lissauer. However, whereas in the cervical and lumbar (fig. 3A) segments there was a sharp transition between the intensely stained lateral and the more faintly reacting medial halves, in the thoracic cord (fig. 4A) a strong reaction was uniformly present throughout the whole lamina.

In *mf* rats the intensity of the immunostaining at all levels (fig. 3B), including thoracic (fig. 4B), was severely reduced and, on occasion, almost completely absent. In the former cases, the reaction product, which was present at the same level of lamina II, was homogeneously present throughout the whole lamina at cervical and lumbar levels,

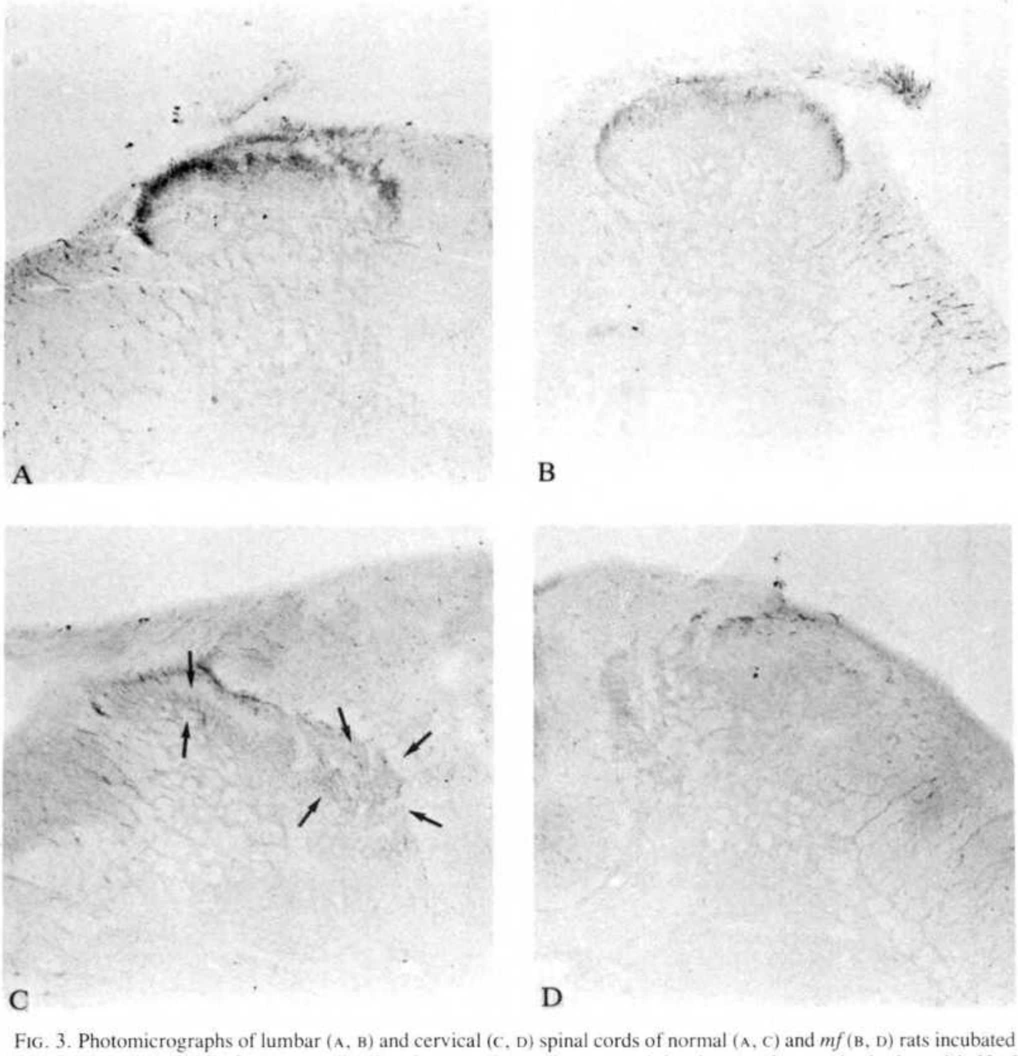

FIG. 3. Photomicrographs of lumbar (A, B) and cervical (C, D) spinal cords of normal (A, C) and *mf* (B, D) rats incubated with TC6 (A, B) and SSEA3 (C, D) antibodies. In normal rats, immunostaining is more intense in the lateral half of the lamina with TC6; in the mutant the lamina is homogeneously but weakly positive. In normal rats, SSEA3 immunostaining is diffusely present in lamina I and in the medial and lateral extremities of laminae III and IV (arrows); only traces of immunostaining are present in laminae III and IV of mutant rats. ×50.

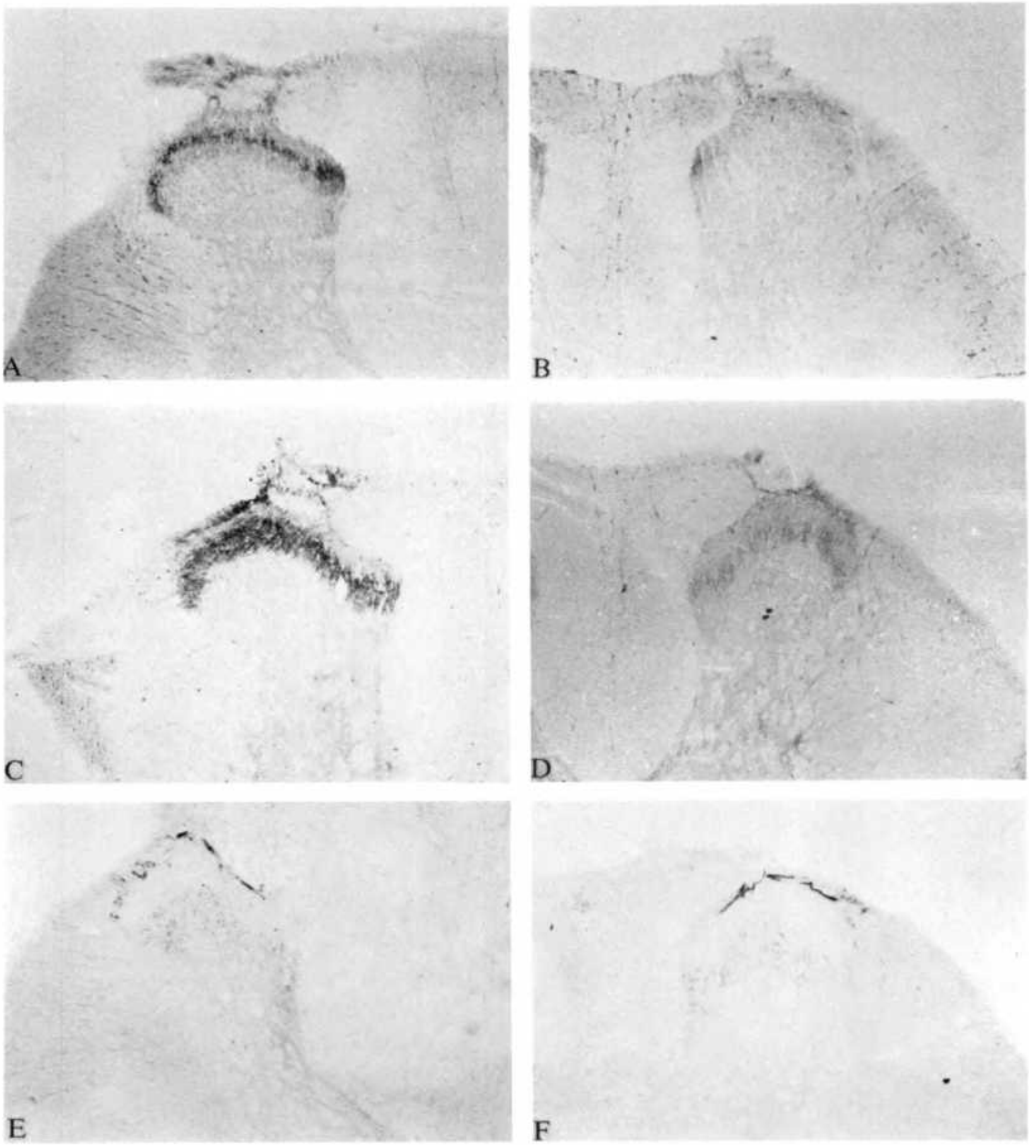

FIG. 4. Photomicrographs of thoracic spinal cord of normal (A, C, E) and *mf* (B, D, F) rats incubated with TC6 (A, B), LA4 (C, D) and SSEA3 (E, F). With the former two antibodies, the cord of the mutants (B, D) shows homogeneously weak reaction. With SSEA3 there is a strong immunoreaction in lamina I in both groups of animals; staining in laminae III and IV of control rats (E) appears as granules which are extremely sparse in the same area in mutants (F). ×50.

although it was more intense in the lateral areas. A more or less intensely stained tract of Lissauer could also be seen.

In normal rats MAb LA4 labelled all the layers of lamina II, although the reaction was most intense in the inner half. Furthermore, in the cervical and lumbar regions, the transition between lateral and medial halves was not as sharp as with the previous antibodies and, on occasion, immunostaining was homogeneously distributed as normally seen at thoracic level (fig. 4C). In most cases, the tract of Lissauer was also stained.

The extent of immunolabelling in the dorsal horn of mutant rats was variable but always extremely reduced and at times almost completely absent and more uniformly distributed throughout the horn than in control rats. The tract of Lissauer was identifiable, mainly in the thoracic segments (fig. 4D).

In normal rats two quite distinct bands of SSEA3 immunostaining could be recognized, one in lamina I, the other involving laminae III and IV (fig. 3C). The former extended throughout the whole lamina and consisted of granular material which in places extended beyond the grey matter into the dorsally placed white matter; the latter was less intense and consisted of aggregates of granular material variously arranged in the laminae. In some of the specimens, SSEA3 positive fibres were also seen in the dorsal funiculi. Similar features were seen in the thoracic cord (fig. 4E).

In lamina I of *mf* rats, immunoreactivity was more intense than in controls (fig. 3D). It was localized on variously arranged filaments with dorsoventral orientation and penetrating into the dorsal white matter. On the other hand, reaction in the deeper laminae was reduced (fig. 4F) and, in places, completely absent.

Morphometric studies

Cell counts. The numbers of cells labelled with the various antibodies in cervical, thoracic and lumbar DRG of control and *mf* rats are shown in the Table. Of the four antibodies used, SSEA3 normally visualizes fewer neurons than the other three. In spite of a considerable individual variability both in the mutant and control groups, the values were higher in the latter and the differences tended to be most striking at cervical and lumbar levels. Expressing the number of ganglion cells in the mutant as percentage

TABLE. NUMBERS OF DRG CELLS IMMUNOLABELLED WITH THE VARIOUS ANTIBODIES IN NORMAL AND *mf* RATS*

	SSEA3		*TC6*		*LD2*		*LA4*	
	N	*mf*	*N*	*mf*	*N*	*mf*	*N*	*mf*
C6			1487	382	548	269	1114	276
C7	248	64	885	440	325	318		
C8	298	133					1037	206
	364	93						
T5					610	524		
T6	78	40	604	499	463	226	1092	341
	197	181			510	198		
T7	119	33	903	626				
	74	25						
T8							723	466
L4	201	59	2884	394			1732	121
							2060	270
L5	612	261			1349	952		
	479	210			1991	1088		

* Values represent the total number of immunoreacting nerve cells in a single DRG and were obtained from a total of 5 mutants and 5 control rats.

of those present at the same level in control rats and plotting scatter diagrams of those values, it can be seen (fig. 5) that values for thoracic ganglia in the *mf* rats are abnormally low, although not to the same extent as in cervical and lumbar ganglia. The differences between the values obtained in mutant and control rats using the various antibodies and at each level were tested statistically using the sign test. In all circumstances cell counts in the DRG of *mf* rats were significantly less than in matched controls (SSEA3: $P < 0.005$; TC6: $P < 0.08$; LD2: $P < 0.03$; LA4: $P < 0.05$; cervical DRG: $P < 0.08$; thoracic DRG: $P < 0.03$; lumbar DRG: $P < 0.02$).

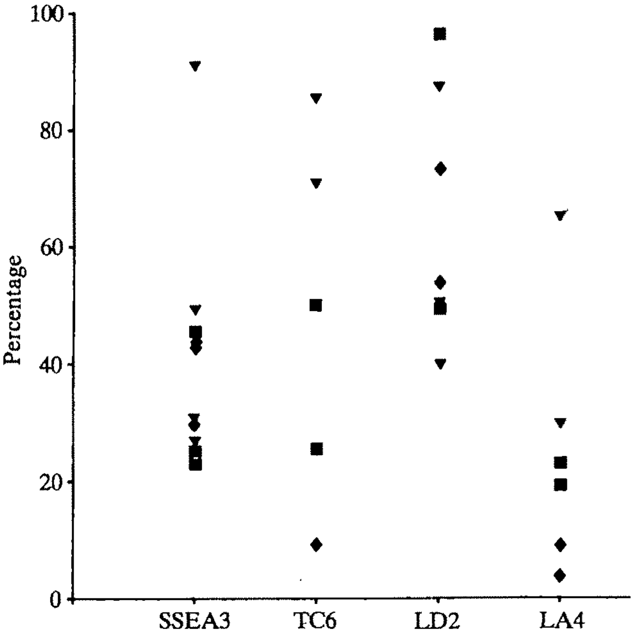

FIG. 5. Nonparametric representation of the percentages of *mf* DRG cells reacting with various antibodies at various levels; squares indicate cervical, triangles thoracic and diamonds lumbar DRG cells.

Cell sizes. The histograms of distribution of the diameters of cells reacting with TC6, LD2 and LA4 antibodies showed similar unimodal patterns with range between 10 and 65 μm and peak at 30 μm (fig. 6). The same distribution was observed in *mf* rats.

Cells immunostained with SSEA3 showed, both in control and mutant rats, the same range of sizes between 10 and 65 μm. However, the distribution of the diameters was, in most cases, bimodal with one peak between 15 and 20 μm and another at 36–40 μm (fig. 7).

DISCUSSION

The use of monoclonal antibodies directed against sensory neuron specific cell surface antigens has made it possible to correlate the morphological and physiological properties

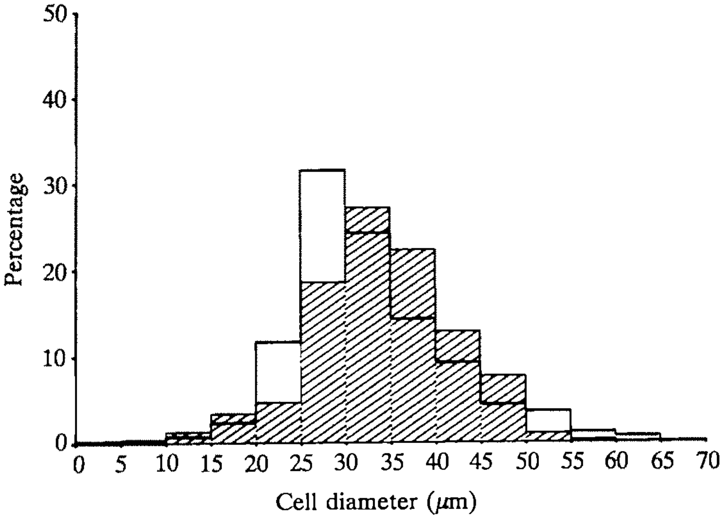

FIG. 6. Frequency distribution of diameters of DRG cells of normal (open) and *mf* (hatched) rats incubated with TC6.

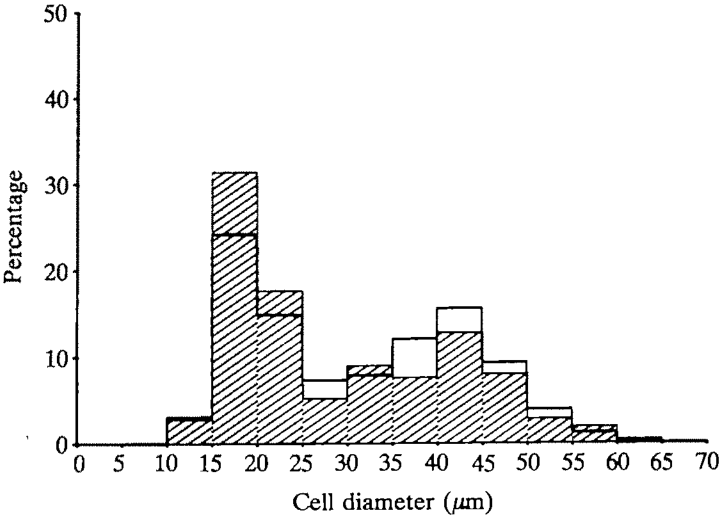

FIG. 7. Frequency distribution of diameters of DRG cells of normal (open) and *mf* (hatched) rats incubated with SSEA3.

of DRG cells with the localization of their terminals in the spinal cord (*see* Jessell and Dodd, 1986). Two families of oligosaccharide structures, globoseries and ganglio/lactoseries carbohydrates, are present in different subsets of sensory cells (Dodd *et al.*, 1984; Dodd and Jessell, 1985; Jessell and Dodd, 1985). Of the globoseries epitopes, which include SSEA3 and SSEA4 and which have similar distribution, the former was investigated in the present study. Of the numerous lactoseries epitopes expressed by

DRG cells, TC6, LD2 and LA4 were investigated. SSEA3 is found in approximately 9% of DRG cells, predominantly those of small and large sizes, none of which coexpresses substance P, somatostatin or FRAP (Dodd *et al.*, 1984). In the dorsal horn of the spinal cord, SSEA3 positive terminals are located in laminae I, III and IV while small bundles of axons may be found also in the dorsal columns (Jessell and Dodd, 1986). In lamina I SSEA3 immunoreactivity may represent high threshold mechanoceptors which are known to terminate in this region (Light and Perl, 1979); positive terminals in laminae III and IV are presumably low threshold mechanoceptors associated with hair follicles (Brown *et al.*, 1977; Ralston *et al.*, 1984).

Monoclonal antibodies to TC6 and LD2 label the same subset of neurons. These represent approximately 25% of DRG cells and are predominantly of small and intermediate sizes. Their axons terminate in a dense band which corresponds to lamina II (Dodd and Jessell, 1985). Neurons which stain with these antibodies do not express substance P; however, those which react with LD2 antibodies coexpress somatostatin and FRAP (Dodd and Jessell, 1985).

LA4 epitope is expressed by 45–50% of small and intermediate DRG neurons. These neurons do not express substance P but there is overlap with somatostatin-positive cells; their terminals are located predominantly in the inner part of lamina II (Dodd and Jessell, 1985).

The distribution of afferent fibres expressing lactoseries determinants in the dorsal horn is consistent with their identification as C fibres (Jessell and Dodd, 1986).

The results of the present study largely confirm the findings of previous investigations on DRG cells of normal rats (Dodd *et al.*, 1984; Dodd and Jessell, 1985). However, when our figures are compared with total numbers of DRG cells obtained in control rats by Jacobs *et al.* (1981) and Scaravilli and Chimelli (1984), the percentage of neurons labelled by each antibody in our study was smaller than in previously published series: only 22% of the neurons were TC6-positive, 11% were LD2-positive and 19% LD4-positive. The overall percentage of SSEA3-positive cells was similar to that reported by Dodd *et al.* (1984), but the values were low at cervical and thoracic levels. While it is possible that different strains of rats used by the various workers may be responsible for the marked difference in number of cells reacting to MAbs, it is more likely that this is due to the different methods used, particularly when dealing with absolute numbers of DRG cells.

The differences in intensity of immunostaining between lateral and medial parts of the dorsal horns of the cervical and lumbar segments obtained with the MAbs TC6, LD2 and LA4 are at variance with the results obtained by previous workers. This cannot be accounted for by the different techniques of visualization, since in the thoracic cord the whole laminae were homogeneously stained. Similar variability has been observed in the distribution of the neurotransmitter substance P: Hökfelt *et al.* (1975) and Wall *et al.* (1981) reported homogeneous distribution in the normal spinal cord of cats and Wistar rats, respectively; on the other hand, Barbut *et al.* (1981) showed in the same strain of rats a denser immunostaining in the median region of the dorsal horn and DiFiglia *et al.* (1982) demonstrated that the lateral part of the cervical dorsal horn in monkeys was more densely stained than the medial.

Some findings of the present investigation can be correlated with the loss of definite sensory modalities in the *mf* rat; indeed, the complete lack of proprioception and the severe deficiency in muscle spindles and pacinian corpuscles, which are among the most characteristic clinico-pathological features in the mutant (Jacobs *et al.*, 1981) are reflected in a low number of positive cells and in the less intense SSEA3 immunostaining of laminae III and IV. As previously mentioned, these laminae are the site of termination of low threshold mechanoceptors.

On the other hand, an unexpected finding in the present investigations was the reduced number of nerve cells reacting with the various antibodies in the thoracic ganglia of *mf* rats as well as the smaller amounts of immunostaining at the same levels of the dorsal horn. Indeed, in these mutants the sensation at thoracic level has been reported as normal (Chimelli and Scaravilli, 1986); the numbers of DRG cells (Scaravilli and Chimelli, 1984), the morphology of the dorsal horn and the amount of substance P at thoracic level (Scaravilli, 1983) have also been described as virtually unaffected. The apparent discrepancy between the results of the previous investigation on substance P (Scaravilli, 1983) and the present study may be due to the fact that none of the oligosaccharides investigated is present in cells coexpressing substance P. Preserved bands of thoracic sensation, described by various authors (England and Denny-Brown, 1952; Ogden *et al.*, 1959; Campbell, 1970) led Nukada *et al.* (1982) to postulate that sensory cells innervating these areas could develop normally. Our results show instead that, in spite of being normal in number and able to sustain an almost normal dorsal horn and to produce normal amounts of substance P, thoracic DRG cells in *mf* rats take part in the mutation as indicated by their inability to produce the oligosaccharides and to transport them to the axon terminals. The fact that the antibodies used covered virtually the whole range of cell sizes further indicates that the abnormality does not spare any subset of cells. Furthermore, since nerve cells of different sizes differentiate from gestational day 11 to 15 (Lawson *et al.*, 1974), these results show that in *mf* rats the expression of the abnormal gene continues throughout the whole period of ganglion cell differentiation.

Previous studies on the *mf* rat (Chimelli and Scaravilli, 1986) left unresolved the question as to whether the reduction in number of sensory cells was due to loss of neurons, mainly of the large ones, or to widespread decrease in number throughout the whole range of diameters with proportional decrease in size of the surviving cells. The results of morphometric studies, showing similar distribution of cell diameters in normal and *mf* rats for each subset of neurons, support the former hypothesis.

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ABNORMAL VIBRATION-INDUCED CEREBRAL BLOOD FLOW RESPONSES IN IDIOPATHIC DYSTONIA

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SUMMARY

Regional cerebral blood flow responses to vibrotactile stimulation were studied in 11 patients with predominantly unilateral idiopathic focal dystonia and 18 normal subjects using PET and $H_2{}^{15}O$. Stimulation produced a consistently localized and robust peak response in primary sensorimotor cortex contralateral to hand vibration in normal subjects (averaged hemisphere response 10.97 ml/(100 g·min) ±2.53). The sensorimotor response in dystonic patients was also consistently localized to the same area, but significantly reduced in magnitude whether vibrating the affected (8.35 ml/(100 g·min) ±2.29) or unaffected hand (8.40 ml/(100 g·min) ±2.15). Furthermore, vibration induced a dystonic cramp in the stimulated arm/hand in 6 patients, but not in any normal subjects. To determine whether the cocontraction of agonist and antagonist muscles could, in itself, attenuate the regional blood flow response, 10 normal subjects were studied with vibration during voluntary cocontraction of appropriate hand and forearm muscles, as well as with vibration alone. Vibration with voluntary cocontraction (mean = 12.57 ml/(100 g·min) ±2.13) produced a significantly greater response than vibration alone (mean = 10.30 ml/(100 g·min) ±2.20, $P < 0.00008$). This abnormal sensorimotor response may have important implications for understanding the pathophysiology of idiopathic dystonia.

INTRODUCTION

Dystonia is a syndrome of intermittent or sustained muscle contraction that frequently causes twisting and repetitive movements producing abnormal postures (Fahn, 1988). Classification schemes of dystonia vary. One method depends upon which part of the body is affected (e.g., focal, segmental or generalized), whereas another approach depends upon identifiable aetiology. In the latter scheme, dystonias with identifiable aetiology are termed secondary dystonias and those without, primary or idiopathic (Calne and Lang, 1988).

The pathophysiological mechanisms underlying either primary or secondary forms of dystonia have remained elusive. Abnormalities of dopaminergic pathways have been implicated by the appearances of dystonic postures in parkinsonian patients treated with excessive doses of L-DOPA and by the occasional development of acute dystonic reactions in patients treated with dopaminergic antagonists, such as neuroleptics or metoclopramide.

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Postmortem investigations have not been helpful in elucidating a pathophysiological basis for idiopathic dystonia (Hedreen *et al.*, 1988), although a recent study has reported variably elevated or depressed levels of monoamines, especially norepinephrine, in a variety of brain regions in 2 patients with dystonia musculorum deformans (Hornykiewicz *et al.*, 1986). Computed tomography (CT) and magnetic resonance imaging (MRI) have permitted identification of lesions in basal ganglia, such as striatal infarcts, in hemidystonic patients (Marsden *et al.*, 1985; Pettigrew and Jankovic, 1985; Obeso and Giménez-Roldán, 1988). Many patients, however, have striatal infarcts and do not develop involuntary movements. The exact characteristics of a lesion, such as size or location, necessary to produce dystonia are not clear.

Positron emission tomography (PET) permits the regional measurement of blood flow in the living human brain (Raichle, 1986). Regional blood flow correlates well with neuronal activity (Raichle, 1987) and can be a useful tool to evaluate regional brain function in patients with dystonia. In this regard, Perlmutter and Raichle (1984), using PET, found increased blood flow and blood volume with decreased oxygen extraction and metabolism in the contralateral basal ganglia in a 50-yr-old man with posttraumatic paroxysmal right hemidystonia. Conventional evaluation, including electroencephalography, CT and cerebral angiography, have been unrevealing in that example of secondary dystonia. Recent advances in PET methodology such as improvements in anatomical localization in PET images (Fox *et al.*, 1985) and subtraction-image analysis (Mintun *et al.*, 1989) have enhanced our ability to evaluate regional brain physiology.

Nevertheless, patients with idiopathic dystonia can have normal regional blood flow in the resting state (Perlmutter and Raichle, 1988). Since these patients frequently have dystonic spasms only with particular actions, we attempted to evaluate brain function during specific manoeuvres. Initially, we asked 2 dystonic patients to open and close their hands repetitively (twice per s) during a blood flow scan. The blood flow response in contralateral sensorimotor cortex was diminished compared with normal subjects (Perlmutter and Raichle, 1988). However, interpretation of these findings was ambiguous as we doubted whether patients could perform the task as vigorously as normal subjects. To avoid this ambiguity, we chose a totally passive activation paradigm, vibrotactile stimulation of a hand. This produces a consistent robust increase in blood flow in contralateral sensorimotor cortex (Fox *et al.*, 1987). Interestingly, we very soon found that hand vibration could produce an obvious spasm of the vibrated hand in dystonic patients, but not in normal subjects (Perlmutter and Raichle, 1988). This dramatic response further suggested that vibrotactile stimulation would be a useful activation paradigm to evaluate whether there is a consistent abnormality in central sensorimotor processing in patients with idiopathic dystonia.

METHODS

We studied 1 left-handed and 10 right-handed patients (4 male, 7 female) between 24 and 70 yrs of age (mean 49, SD 16) with predominantly unilateral dystonia. All patients were rated on the Abnormal

Involuntary Movements Scale (AIMS; Guy, 1976). None of the patients had other clinical neurological abnormalities or laboratory evidence of an underlying disease. All had normal CT brain scans. Table 1 lists the patients' characteristics.

We also studied 14 right-handed, 3 left-handed and 1 ambidextrous control subjects (11 men, 7 women) between 20 and 39 yrs of age (mean 24.6, SD 4.7). None had evidence of neurological disease. Five control subjects took one of the following medications: pseudoephedrine (Sudafed) (none for at least 12 h prior to study), tetracycline for acne, beclomethasone inhaler for pollen allergies (1 puff each morning), contraceptive pills (Ortho-Novum 1/35), and phentermine for appetite suppression (none for 24 h prior to study).

PET studies were performed with the PETT VI system in the low resolution mode (Ter-Pogossian *et al.*, 1982; Yamamoto *et al.*, 1982). Data were recorded simultaneously for 7 slices with a centre-to-centre separation of 14.4 mm. In-plane (i.e., transverse) reconstructed resolution is about 16–18 mm in the centre of the field of view and axial resolution is about 14 mm at the centre.

Subject preparation included the percutaneous insertion of a radial arterial catheter under local anaesthesia, to permit frequent sampling of arterial blood, and insertion of an intravenous (i.v.) catheter for isotope injection in the opposite arm. The head was positioned with a special headholder that used an individually moulded plastic face mask to prevent movement during the study. A laser permanently attached to the wall projected a line onto the mask that corresponded to the position of the lowest PET slice. A lateral skull radiograph with this line marked by a radio-opaque wire provided a record of the subject's exact position in relation to the PET slices (Fox *et al.*, 1985). The overlapping position of radio-opaque markers placed in the external auditory canals confirmed that the head was not rotated about the anteroposterior or vertical axes. After the head was in place, a transmission scan used for individual attenuation correction

TABLE 1. DYSTONIC PATIENTS: CHARACTERISTICS

Case	*Sex*	*Age (yrs)*	*Handedness*	*Diagnosis**	*Duration of symptoms (yrs)*	*Medication*
1	F	70	R	Idiopathic L upper limb	10	
2	M	32	R	Idiopathic torsion dystonia	21	Diazepam, L-DOPA, trihexyphenidyl
3	M	34	R	Dystonic writer's cramp	8	
4	F	42	R	Simple writer's cramp	5	
5	M	57	L	Dystonic writer's cramp	26	
6	F	58	R	Idiopathic, lower limbs**	1.5	
7	M	70	R	Simple writer's cramp	2	
8	F	67	R	DOPA-sensitive hemidystonia	45	L-DOPA/carbidopa
9	F	50	R	Dystonic typist's cramp	0.5	
10	F	24	R	Simple writer's cramp	1.5	
11	F	38	R	Dystonic typist's cramp	5	

* Writer's and typist's cramp are classified as simple (involvement only with writing or typing, respectively) or dystonic (involvement with writing or typing, as well as other fine motor tasks) as defined by Sheehy and Marsden (1982). Medications were withdrawn for 12 h prior to the PET study in Case 2 and 24 h in Case 8. ** This very unusual patient with onset of idiopathic dystonia in the lower limbs at age 56 yrs does not have evidence of parkinsonism after 3.5 yrs. Serum caeruloplasmin, slit lamp ocular examination and repeated MRI of the brain have not revealed abnormalities.

was performed with a ring source of activity containing $^{68}Ge/^{68}Ga$. During each PET scan, the room was darkened and the subject's eyes were closed. The ears were not occluded. Ambient room noise during the scans was almost entirely from cooling fans for the electronic equipment.

Cerebral blood flow (CBF) was measured using a 40 s emission scan following the i.v. bolus injection of about 10 ml of saline containing 55–80 mCi of ^{15}O-labelled water (Herscovitch *et al.*, 1983; Raichle *et al.*, 1983). The short half-life (122 s) of ^{15}O permitted up to 9 repeated measurements in a single study session for each subject.

All dystonic patients had measurements of CBF in the resting state and then repeat measurements during vibrotactile stimulation (Fox *et al.*, 1987; 130 Hz, 2 mm amplitude, Daito Model 91, Higashi, Osaka, Japan) to all 5 finger pads of either both hands simultaneously (Cases 1–5) or sequentially with interposed resting-state scans (Cases 6–11). Stimulation was initiated at the time of bolus injection of the radiotracer and continued throughout the 40 s scan. Each subject was specifically instructed to relax with eyes closed and not to grasp the vibrator (passive vibration). Cases 9, 10 and 11 had 2 complete studies each (Table 2). Repeat studies were not included in comparisons between dystonic patients and normal subjects.

All normal controls had measurements of CBF in the resting state and then repeat measurements during similarly applied passive vibrotactile stimulation applied sequentially to each hand with interposed resting-state scans. Additionally, 10 of the controls had scans under several stimulus conditions: (1) passive vibration of either hand; (2) voluntary contraction of flexors and extensors of the arm, forearm, hand and digits unilaterally ('cocontraction' state) to mimic induced postures seen in dystonic subjects, as discussed below; (3) cocontraction with vibrotactile stimulation and (4) interposed resting-state scans.

These studies were approved by the Human Studies Committee and the Radioactive Drug Research Committee (United States Food and Drug Administration) of the Washington University School of Medicine. Written informed consent was obtained before each PET study.

Data analysis

Global CBF values were calculated for each scan using a 'whole slice' method (Perlmutter *et al.*, 1985). A template for each slice was made using the appropriate rest-state scan by removing all pixels at the

TABLE 2. STUDY CHARACTERISTICS

Case	*Side of dystonia*	*Side of radial arterial line*	*Stimulus**	*Clinical response to vibration***
1	L	R	Bilat.	LUL cramp
2	L > R	R	Bilat.	LUL cramp
3	R	L	Bilat.	Mild RUL cramp
4	R	L	Bilat.	Bilat., mild UL cramps
5	L > R	R	Bilat.	–
6	L > R	R	Unilat.	–
7	R	L	Unilat.	–
8	R	L	Unilat.	RUL cramp
9	R	L	Unilat.	RUL cramp
10	R	R	Unilat.	–
11	L	R	Unilat.	–

* A bilateral stimulus is a vibrotactile stimulus applied to the finger pads of both hands simultaneously from the time of injection of $H_2{}^{15}O$ throughout the 40 s scan. A unilateral stimulus is a vibrotactile stimulus similarly applied singly to each hand during sequential scans with interposed resting-state scans. ** LUL, RUL and bilat. UL represent left upper limb, right upper limb and bilateral upper limbs, respectively. Some patients developed vibration-induced cramps during the PET study, as noted. All these cramps involved the simultaneous contraction of flexors and extensors of the forearm and hand. Cases 9–11 had 2 complete studies each and demonstrated no significant difference from one study to the next. Case 9 developed RUL cramp during both studies. The repeat studies were not included in the comparisons between the dystonic and normal subjects.

edges of the slice with values less than 40% of the peak blood flow value. This same template was applied to all subsequent scans in that study. The mean value for all remaining pixels defined the global CBF for each scan. The global value for each scan then was normalized to 50 ml/(100 g·min) to diminish effects of global fluctuations in CBF. For each control-activation pair, the control scan was subtracted from the activation scan on a pixel-by-pixel basis to yield regional changes in CBF. An automatic computerized search routine of this subtraction image found the brain regions with increases in CBF (Mintun *et al.*, 1989). The magnitudes of the responses were calculated in normalized units of ml/(100 g·min). The anatomical location of the peak response in normal subjects was identified in a standardized stereotactic atlas (Talairach *et al.*, 1967) and was in sensorimotor cortex (*see* below). The corresponding sensorimotor response for dystonic patients was similarly identified. Our anatomical localization technique is independent of the appearance of the physiological images (Fox *et al.*, 1985) and considers individual differences in skull and brain sizes by the use of proportional coordinates as well as adjusting for differences in head placement within the scanner as recorded by a lateral skull radiograph.

The primary aim of this study was to compare responses in dystonic versus normal subjects with respect to location (in 3 axes), as well as magnitude of response. This generated 4 separate comparisons each done by one-way analysis of variance (ANOVA) to determine whether there was a statistically significant difference among any of the means (dystonic and normal subjects) within these groups. Bonferroni's correction for multiple comparisons was used to define a significant P value for each ANOVA as 0.0125 (= 0.05/4). Secondary analyses also were corrected separately for multiple comparisons depending upon the number of statistical tests performed.

Data were analysed separately for bilaterally stimulated and unilaterally/sequentially stimulated patients. The sensorimotor response was always in the hemisphere opposite to the side of the applied stimulus. Thus for a patient with predominantly right-sided dystonia (2/5 of bilaterally stimulated, 4/6 of unilateral/sequentially stimulated), a stimulus applied to the 'ipsilateral' (right) hand would always produce a sensorimotor response in the 'contralateral' (left) hemisphere. Similarly, a stimulus applied to the (relatively uninvolved) 'contralateral' (left) hand would always produce a sensorimotor response in the 'ipsilateral' (right) hemisphere. Because the dystonic subjects had both right and left-sided dystonia, both 'contralateral' and 'ipsilateral' hemisphere responses include right and left hemisphere values and thus were compared with a single averaged right and left magnitude response for each of the 18 normal subjects.

Global CBF values in the resting and activated states and regional CBF values in the resting state for patients and controls were also compared by one-way ANOVAs.

RESULTS

Mean global CBF values (±SD) in the resting and activated states for normal subjects and patients were calculated (normal subjects: at rest, 46.0 ml/(100 g·min) ± 12.1; with vibration, 45.7 ml/(100 g·min) ± 12.0; and with vibration + cocontraction, 41.4 ml/(100 g·min) ± 7.1; dystonic patients: at rest, 39.0 ml/(100 g·min) ± 5.1; and with vibration, 41.1 ml/(100 g·min) ± 4.8). There is no statistically significant difference between any of these values as demonstrated by ANOVA: F = 1.88, $P = 0.119$, total degrees of freedom (df) = 115. Furthermore, there was no significant difference in resting-state regional CBF values for sensorimotor cortex between normal subjects and dystonic patients (normal subjects: left, 55.4 ml/(100 g·min) ± 4.3; right, 56.2 ml/(100 g·min) ± 4.9; dystonic patients: contralateral, 53.3 ml/(100 g·min) ± 4.6; ipsilateral, 53.7 ml/(100 g·min) ± 6.9; ANOVA: F = 1.09, $P = 0.362$, total df = 57). Each of these resting-state regional values was obtained from normalized (global flow = 50 ml/(100 g·min)) scans and represents mean pixel values from 4 pixel-square regions (1 pixel = 0.27 cm × 0.27 cm × 1.4 cm).

Vibrotactile hand stimulation in normal controls produced a marked and consistent increase in regional CBF in the contralateral primary sensorimotor region. The stereotactic atlas coordinates describing the locations of these individual responses were very close together (fig. 1). The response in this location was the peak response in 55/56 rest-activation pairs. In 1/56, the peak response was in high anterior, ipsilateral cerebellum near the midline with a contralateral sensorimotor response being the second greatest response. In this subject, however, the magnitudes of these 2 responses were nearly identical (7.68 and 7.25 ml/(100 g·min), respectively). Mean (±SD) coordinates of the sensorimotor responses are shown in fig. 1 and values given in Table 3. Subgroup analysis in 10 normal subjects showed that side of stimulation with respect to placement (left or right wrist) of the radial arterial catheter did not significantly affect peak-response locations or magnitudes of responses (ANOVAs: for left-right axis, F = 0.689, $P = 0.572$, for anteroposterior axis, F = 0.374, $P = 0.773$, for vertical axis, F = 0.414, $P = 0.745$, for magnitude of responses F = 1.641, $P = 0.220$, where each ANOVA has a total df = 19). Furthermore, the addition of voluntary cocontraction did not alter the location of the maximal response (Table 3).

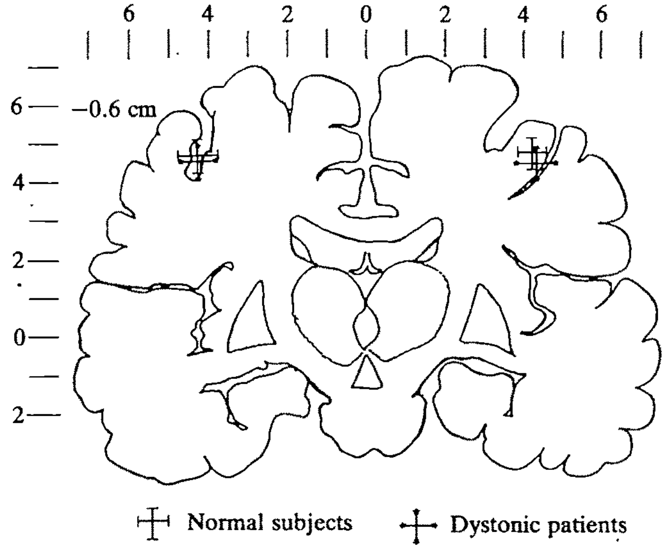

FIG. 1. Mean coordinates for the sensorimotor responses to vibration of the opposite hand in normal and dystonic subjects are shown on this modified coronal brain section (Plate LXXIX from the Talairach Atlas; Talairach *et al.*, 1967). The left hemisphere is on the left. Error bars correspond to 1 SD. Individual responses are always found in cortex, not in the sulcus. The response in dystonic patients 'contralateral' to the greatest affected side is displayed in the left hemisphere. Similarly, the 'ipsilateral' response in dystonic patients is displayed in the right hemisphere. This coronal brain section lies 0.6 cm posterior to the origin of the bicommissural coordinate system (the point midway between the anterior and posterior commissures) and corresponds to the mean anteroposterior axis coordinate of the hand responses. This is just posterior to the central sulcus at this level.

Vibrotactile hand stimulation in dystonic patients also produced a consistent increase

TABLE 3. STEREOTACTIC ATLAS COORDINATES*

	n	*Vertical*	*Left-right*	*Anteroposterior*
Dystonics				
Contralateral	11	4.60 (0.44)	4.28 (0.49)	−0.71 (0.74)
Ipsilateral	11	4.51 (0.40)	4.33 (0.52)	−0.64 (0.28)
Normals				
Vibration alone				
Left	18	4.71 (0.39)	4.31 (0.51)	−0.58 (0.84)
Right	18	4.72 (0.38)	4.21 (0.36)	−0.57 (0.84)
Vibration + cocontraction				
Left	10	4.86 (0.40)	3.95 (0.54)	−0.60 (0.45)
Right	10	4.85 (0.37)	3.94 (0.33)	−0.52 (0.36)
ANOVA		F = 1.269 $P = 0.287$	F = 1.677 $P = 0.151$	F = 0.108 $P = 0.990$

* Locations of vibration-induced blood flow responses have been identified with a stereotactic technique (Fox *et al.*, 1985) that provides standard atlas coordinates (Talairach *et al.*, 1967). Coordinates (mean and SD (bracketed)) are expressed in cm. 'Contralateral' and 'ipsilateral' denote hemisphere lateralization with respect to side of predominant dystonic signs. 'Left' and 'right' indicate left and right hemispheres, respectively. Dystonic patients had vibrotactile stimulation alone, as did 18 normal subjects. Additionally, 10 normal subjects had vibration during voluntary cocontraction of agonist and antagonist muscles of the stimulated upper limb. n = number of individual scans. ANOVA was performed on each column of data. Since there are 4 variables in this study (x, y and z coordinates of response and magnitude of response), statistical significance is defined as 0.05/4 = 0.0125, to adjust for multiple ANOVAs. Resultant F statistics and P values are indicated and do not reach significance.

of regional CBF in the contralateral primary sensorimotor region in *every* case whether stimulated simultaneously on both hands ('bilateral', 5 patients), or sequentially on one hand during one scan and then on the other hand in a subsequent scan during the same study session ('unilateral', 6 patients; Table 2). In these patients with predominantly unilateral dystonia, locations and magnitudes of responses are noted with respect to their greater affected side. The coordinates of homologous locations of responses in sensorimotor cortex did not differ significantly whether 'contralateral' or 'ipsilateral' to the dystonic side or whether bilaterally or unilaterally stimulated. The locations of the responses did not differ significantly between normal subjects and dystonic patients (Table 3). Although the *centre* of the response lies just posterior to the central sulcus in the postcentral gyrus (i.e., primary somatosensory cortex), the entire region of brain that produces this response probably also includes some of the precentral gyrus (i.e., primary motor cortex). Thus we refer to this response as a sensorimotor response. As opposed to the location of the responses, the mean magnitude of response was significantly reduced for the 'contralateral' side compared with the peak response in normal subjects (Table 4).

Surprisingly, the mean magnitude of the response in sensorimotor cortex was also significantly reduced in the 'ipsilateral' hemisphere (i.e., stimulation of the relatively uninvolved side of the body and response identified in the opposite hemisphere; Table 4). There was no statistical difference between the 'ipsilateral' or 'contralateral' response magnitudes. Similarly, no significant differences in magnitude of response resulted from

TABLE 4. MAGNITUDE OF RESPONSE*

	n	*Mean*	*SD*	*Range*
Dystonics				
Contralateral	11	8.35	(2.291)	3.66–10.88
Ipsilateral	11	8.40	(2.154)	3.56–11.03
Normals	18	10.97	(2.039)	6.86–15.32

ANOVA F = 7.26; $P = 0.00220$

* Magnitudes of sensorimotor cortex blood flow responses opposite to the side of hand vibration were obtained by activation vs rest subtraction-pair analysis (Mintun *et al.*, 1989) and are expressed in normalized units of ml/(100 g·min). The mean value, SD and range of response magnitudes are given for 11 dystonic and 18 normal subjects. 'Contralateral' and 'ipsilateral' denote hemisphere lateralization with respect to side of predominant signs of dystonia. Normals include responses in right and left hemispheres. n = number of individual responses. Since 4 variables (x, y and z coordinates of response and magnitude of response) were compared, statistical significance is defined as 0.05/4 = 0.0125 to adjust for 4 ANOVAs. The ANOVA, F statistic and P value for magnitude of response are shown above and demonstrate significant differences among the 3 groups. Post hoc, 2-tailed, unpaired t tests revealed significant differences between contralateral as well as ipsilateral hemisphere responses in dystonic vs normal subjects ($P = 0.00353$; $P = 0.00329$, respectively).

bilateral (mean 9.14 ml/(100 g·min) ± 1.98) or unilateral (mean 7.74 ml/(100 g·min) ± 2.19) vibrotactile stimulation, $P = 0.137$ by 2-tailed, unpaired t test.

Finally, vibrotactile stimulation induced an obvious cocontraction of flexors and extensors in the digits, hand and forearm of the stimulated extremity in approximately half (6/11) of the dystonic patients, but none of the normal controls (Table 2). There were, however, no significant differences in magnitudes of either ipsilateral or contralateral responses between patients who developed cocontraction and those who did not (ANOVA: F = 1.437, $P = 0.265$, total df = 21). To investigate further the effect of muscle activity on the magnitude of response, 10 normal controls additionally performed a similarly appearing voluntary posture during vibrotactile stimulation of each hand separately. In each case, the maximal response remained in contralateral sensorimotor cortex and in 18/20 rest-activation pairs the magnitude was larger than vibration alone (vibration during cocontraction: mean = 12.57 ml/(100 g·min) ± 2.13, vibration alone: mean = 10.30 ml/(100 g·min) ± 2.20, $P < 0.00008$ by 2-tailed, paired t test).

DISCUSSION

We find that vibrotactile stimulation of the hand produces a diminished regional blood flow response in sensorimotor cortex in patients with unilateral dystonia. Surprisingly, the hemisphere ipsilateral, as well as contralateral, to the involved side of the body demonstrates this attenuated response. These data suggest that our dystonic patients have an abnormality of central sensorimotor processing. It is important, however, to consider methodological and biological factors that could influence the interpretation of these findings.

One must consider technical factors that could have diminished the magnitude of the blood flow response in the dystonic patients. For example, if sensorimotor cortex was near maximally stimulated in the resting-state because of involuntary movements, then subsequent increases produced by further activation, such as vibrotactile stimulation, could be limited. Such an explanation for our findings, however, seems unlikely. Most subjects had action dystonia and none had dystonic postures during the resting-state scans. More importantly, resting blood flow for the sensorimotor region was not significantly different between dystonic and normal subjects.

Another source of an artefactually lower magnitude of response could occur if global CBF in dystonic patients was significantly higher than in normal subjects in the resting state. If this were true, then the same absolute increase in regional CBF with activation would appear smaller. This was not the case. Resting-state mean global flows were not significantly different between dystonic patients and normal subjects, although there was a wide range of values in both groups.

Another consideration is whether there may have been consistent global shifts in blood flow with activation. Again, global flows during activation showed a wide range of values in both normal and dystonic subjects, but there was no significant difference between the two groups. Furthermore, voluntary cocontraction did not produce a global CBF change in normal subjects. Thus the activation paradigm did not cause a differential shift in *global* blood flow (larger shifts for normal subjects or smaller shifts for dystonic patients) that could explain the diminished *regional* response in the dystonic patients.

Patients with idiopathic focal dystonias have cocontraction of agonist and antagonist muscles as recorded by electromyography (Cohen and Hallett, 1988). In the stimulated extremity of approximately half (6/11) of the dystonic patients, vibration induced clinically apparent cocontractions of agonist and antagonist muscles similar in appearance to dystonic spasms. They developed almost immediately after starting vibration and lasted for the duration of the stimulus. The spasms occurred only in the exclusively or predominantly dystonic side whether the patient was vibrated simultaneously on both hands (3/5) or unilaterally on the involved side (2/6), except in one right-handed dystonic patient (Case 4). That patient developed mild bilateral spasms during bilateral stimulation. Clinically obvious spasms did not occur in any normal subject. Neither patients nor normal subjects had electromyographic monitoring during vibrotactile stimulation to determine whether subclinical muscle contractions were present. The presence or absence of muscle spasms could be relevant to our findings if it were hypothesized that, if present, the spasms could diminish the evoked blood flow response to vibration. This would be analogous to the so-called 'gating' effect that occurs at a spinal or lower central level (Rushton *et al.*, 1981; Desmedt, 1983; Starr and Cohen, 1985; Cohen and Starr, 1987; Tapia *et al.*, 1987).

To determine the effect of cocontraction on the vibration-induced evoked blood flow response, 10 normal subjects performed a voluntary cocontraction of flexors and extensors to produce a posture that mimicked that seen in dystonic patients during vibrotactile stimulus. In each case the maximal response to vibrotactile stimulation with voluntary cocontraction remained in contralateral sensorimotor cortex and, in 18/20 rest-activation pairs, the magnitude was larger than with vibration alone (*see* Results). In the other 2 subjects the magnitudes of responses to vibration with cocontraction were similar to vibration alone. This demonstrates that voluntary muscle contraction did not diminish the vibration-induced blood flow response. We recognize, however, that voluntarily produced muscle spasms may not be an exact replica of vibration-induced involuntary muscle spasms.

It also should be noted that the mean age of the dystonic patients was older than the normal volunteers. If the vibration-induced evoked blood flow response decreases with age, our results could reflect this age-related difference. We have found previously that measurements of resting-state CBF obtained by a method that minimizes contributions from nonbrain structures do not correlate with age (Perlmutter *et al.*, 1985). Nevertheless, these resting-state data do not indicate whether the blood flow response to activation decreases with age. In the present study, age of the 18 normal subjects did not correlate with the magnitude of response (correlation coefficient = -0.16, $P = 0.54$). However, their ages only ranged from 20 to 39 yrs which could be inadequate to demonstrate a potential threshold of diminished response. Within the group of dystonic patients, ages ranged from 24 to 70 yrs. Again, age did not correlate with the magnitude of response, whether contralateral or ipsilateral to the side of dystonia ($r = 0.69$, $P = 0.02$ and $r = 0.46$, $P = 0.15$, respectively, where Bonferroni correction for multiple correlations yields significance at $P < 0.05/3 = 0.0167$). Although not significant, there is a trend for an increased response with increased age in the dystonic patients, that is, just the opposite of what one would predict if age accounted for our diminished response in dystonic vs normal subjects. Finally, subgroup analysis was performed for those dystonic patients ($n = 4$) within the age range of the normal subjects. These dystonic patients did not differ in magnitude of responses from the larger group of all dystonic patients for either the ipsilateral or contralateral hemisphere responses (ANOVA: $F = 0.992$, $P = 0.412$, total df = 29), but were significantly different from normal subjects (ANOVA: $F = 9.604$, $P = 0.000929$, total df = 43). This was true both for the ipsilateral response vs normal subjects and for the contralateral response vs normal subjects (post hoc, two-tailed, unpaired t tests: $P = 0.00904$ and $P = 0.000620$, respectively). For these reasons, we believe it is unlikely that the diminished magnitude of response seen in dystonic patients reflects an age-related difference.

Medications used to treat dystonia conceivably could have affected global blood flow or vascular reactivity, thus diminishing the blood flow response to vibration. Only 2/11 dystonic subjects were taking medication; Case 2 took no medication for 12 h, Case 8 took none for 24 h, prior to the PET study (Table 1). Furthermore, the global flows in these 2 patients, both at rest and with activation, as well as the resting-state blood flow in the sensorimotor region, were not significantly different from the mean values for the other patients.

Surprisingly, the vibration-induced blood flow response was diminished bilaterally in the patients despite exclusively (8/11) or predominantly (3/11) unilateral clinical involvement. One might question whether these findings reflect difficulty in applying vibrotactile stimulation on the same side as the arterial catheter, thereby producing a diminished blood flow response in the opposite hemisphere. In support of this notion, the arterial catheter had been placed in the arm opposite to the side of dystonia in 10/11 patients. This raises further concern that inadequately applied vibration of the relatively normal side spuriously produced a diminished response in the hemisphere 'ipsilateral' to the dystonia. However, this does not seem likely since placement of the arterial catheter on the left or right side did not produce a significant difference in the magnitude of response to vibration of either hand in normal subjects (*see* Results).

Further interpretation of these bilateral findings must consider the nature of the clinical symptoms in the patients. Did the patients have truly unilateral disease? Each patient was evaluated carefully at the time of the PET study and rated on the AIMS (Guy, 1976). Based on clinical evidence, 3 of the 11 were predominantly, but not exclusively, unilateral. The remainder were exclusively unilateral. It is possible that some of these latter 8 patients could develop clinically overt bilateral signs in the future and might have harboured unapparent subclinical abnormalities at the time of the PET study. It would be helpful to know how often patients with focal dystonia develop dystonia on the other side of the body. Several studies have investigated the natural history of patients with focal dystonias. In an extensive follow-up of 91 patients with isolated idiopathic focal dystonia (writer's cramp) Sheehy *et al.* (1988) noted that 33% (30/91) changed hands for writing. Seven of these 30 (23.3%), or 7.7% of the total group, developed dystonia in the other hand, an average of 6 yrs later (range 1 – 11 yrs). That study excluded those who developed dystonia in other parts of the body and therefore does not provide an answer to our specific question. However, in a more recent study of 34 patients collected in 1980, with follow-up of 20 for at least 6 yrs, only 1 (5%) developed dystonic writer's cramp of the opposite hand and none developed evidence of dystonia elsewhere (Sheehy *et al.*, 1988). In 1 of 9 (11%) patients presenting with isolated typist's cramp, dystonic writer's cramp developed in the contralateral hand. None developed evidence of dystonia elsewhere (Sheehy *et al.*, 1988). Thus an initial idiopathic focal dystonia such as writer's or typist's cramp might be expected to progress to other areas in about 5 – 11%. This would not apply to hemidystonia or to segmental, multifocal or generalized dystonia. After a minimum of 1½ yrs of follow-up, only 1 (Case 6) of our 8 patients with exclusively unilateral symptoms at the time of the PET study subsequently developed dystonia on the opposite side and she did so within 1 month of her PET scan.

Based on the foregoing considerations, we are confident that these results represent a true bilateral abnormality in the vibration-induced evoked blood flow response in sensorimotor cortex of these patients with idiopathic unilateral dystonia. A unilateral abnormality might have been anticipated in patients with hemidystonia secondary to an identifiable contralateral basal ganglia lesion, although we did not include such patients in our study.

There are several observations that suggest that patients with idiopathic dystonia could have an abnormality of central sensorimotor processing. Nearly all our patients have action dystonia, that is, dystonia not present at rest but only (or predominantly) with highly specific movements (e.g., dystonia might occur on typing, but not on tapping the fingers). One possible pathophysiological mechanism could be an abnormality in input to, or feedback from, central sensorimotor areas that could explain this discrimination between two such similar motor tasks. This would be consistent with the observed decrease in the vibration-induced blood flow response in the sensorimotor area. This is also consistent with the observation that patients with idiopathic dystonia describe 'sensory tricks', whereby simply touching a specific body part will temporarily diminish or eliminate the dystonic spasm. In contrast, we observed that hand vibration caused an obvious spasm of the vibrated arm and hand similar to involuntary dystonic cramps. In both cases, sensory tricks and hand vibration, the clinical effects could reflect an abnormal motor response to sensory input.

The decreased vibration-induced blood flow response in sensorimotor cortex may also provide further insights into the pathophysiological mechanisms for dystonia. In general, blood flow or metabolism reflects activity of neuronal terminal fields rather than cell bodies (Schwartz *et al.*, 1979). Therefore, the decreased response in sensorimotor cortex could represent a decrease in activity in neurons that project to sensorimotor cortex or, alternatively, in local interneurons. Recent evidence from anatomical tracing techniques and physiological investigations suggests that discrete somatotopically and functionally organized basal ganglia-thalamo-cortical circuits exist (Collins and Divac, 1984; Alexander *et al.*, 1986). The motor circuit has cortical input to striatum from motor, somatosensory, supplementary motor and arcuate premotor areas (Künzle, 1975, 1977; Alexander *et al.*, 1986). These inputs retain discrete and progressively integrated pathways through striatum, globus pallidus, substantia nigra and thalamus, ultimately projecting back to a specific area, supplementary motor cortex, and from there to arcuate premotor and motor areas (Alexander *et al.*, 1986; Penney and Young, 1986; fig. 2). The somatotopic functional units may correspond to anatomical and histochemical discontinuities also recently identified in striatum. Islands of cells, called 'striosomes' by Graybiel *et al.* (1981), are surrounded by striatal tissue known as matrix. Neurons within striosomes and matrix have different interconnections (Graybiel and Ragsdale, 1983; Penney and Young, 1986).

Penney and Young (1986) believed that striatal inhomogeneities provide a framework for interpretation of the pathophysiology of movement disorders and have proposed a specific model that could explain the clinical similarities and differences between Parkinson's disease and Huntington's disease. Dystonia, with its involuntary intermittent spasms of agonist and antagonist muscles, could be analysed in a fashion similar to chorea. Both exhibit excessive unwanted movements. Furthermore, patients with *secondary* forms of dystonia frequently have identifiable lesions within the striatum (Perlmutter and Raichle, 1984; Marsden *et al.*, 1985; Pettigrew and Jankovic, 1985; Obeso and Giménez-Roldán, 1988). Perhaps in these cases of documented striatal pathology, there is predominantly a defect in matrix neurons of the striatum, selectively projecting to the globus pallidus externa (GP_e). This selective matrix neuronal loss, similar to that proposed for Huntington's chorea (Penney and Young, 1986), would disinhibit GP_e neurons with subsequent excessive inhibition of subthalamus. This, in turn, could decrease subthalamic excitatory input to the globus pallidus interna (GP_i)

and substantia nigra pars reticulata (SN_r) that normally would suppress unwanted movements.

The cause of dystonia in patients with idiopathic disease may be very different. Our finding of a decreased vibration-induced blood flow response in sensorimotor cortex in these patients fits well into the above-mentioned scheme describing the cortico-striato-pallido-thalamo-cortical circuit. The decreased response suggests decreased terminal field neuronal activity in sensorimotor cortex. This could then result in decreased excitatory transmission from this region to matrix neurons of the striatum (Ragsdale and Graybiel, 1981; Goldman-Rakic, 1982; Graybiel and Ragsdale, 1983; Selemon and Goldman-Rakic, 1985; Penney and Young, 1986). Decreased excitatory input from sensorimotor cortex could have the same functional result as the proposed striatal matrix defect in Huntington's disease (Penney and Young, 1986) or our postulated mechanism in secondary dystonias associated with striatal lesions. That is, it could produce disinhibition of GP_e, subsequent excessive inhibition of subthalamic neurons and finally decreased subthalamic excitatory drive of GP_i and SN_r that normally would suppress abnormal involuntary movements (i.e., in this instance, dystonic postures). A primary defect, then, might reside in sensorimotor cortex.

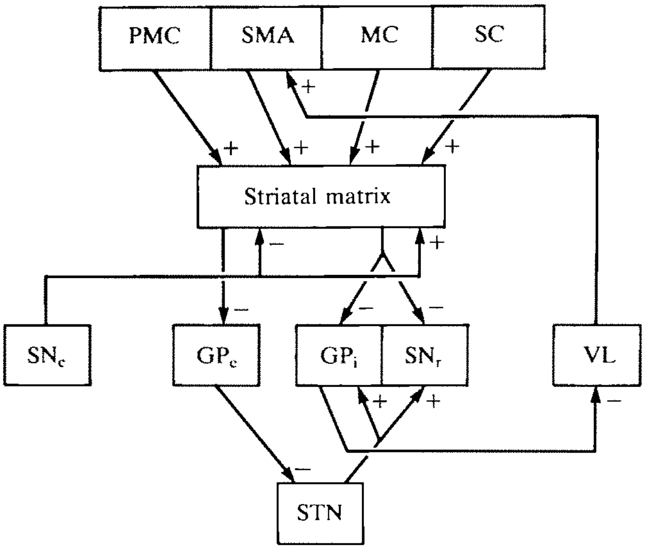

FIG. 2. This is a simplified schematic diagram of the connections of the cortico-striatal-pallidal-thalamo-cortical motor circuit (Alexander *et al.*, 1986; Penney and Young, 1986). Connections are indicated by arrows: + = excitatory, − = inhibitory. MC = primary motor cortex; SMA = supplementary motor cortex; PMC = premotor cortex; SC = somatosensory cortex; GP_e = globus pallidus externa; GP_i = globus pallidus interna; SN_r = substantia nigra pars reticulata; SN_c = substantia nigra pars compacta; STN = subthalamic nucleus; VL = ventral lateral thalamus. A significantly decreased vibration-induced cerebral blood flow response in sensorimotor cortex (SC/MC) was found both contralateral and ipsilateral to the most affected side in 11 patients with predominantly unilateral idiopathic focal dystonia. We suggest that this is indicative of decreased excitatory transmission from this region to matrix neurons of the striatum. This, in turn, could produce disinhibition of GP_e, subsequent excessive inhibition of subthalamic neurons and finally decreased subthalamic excitatory drive of GP_i and SN_r that normally would suppress abnormal involuntary movements.

Alternatively, the decreased blood flow-evoked response in sensorimotor cortex could reflect a 'downstream' effect from altered output at another point in the basal ganglia-thalamo-cortical circuit. The primary defect could be in regions such as the striatum, pallidum, thalamus, or supplementary motor area, as long as the subsequent defect would produce decreased activity in sensorimotor cortex consistent with our findings. Additionally, modulation of the cortico-striato-pallido-thalamo-cortical circuit via other pathways, either not discussed in our simplified presentation or not yet known, could produce decreased subthalamic excitatory drive of GP_i and SN_r that normally would suppress unwanted, involuntary movements.

We anticipate being able to investigate other areas of brain such as the supplementary motor area, cerebellum and, possibly, thalamus. However, to evaluate lower magnitude responses requires studying larger numbers of dystonic patients with relatively more homogenous clinical characteristics (e.g., all right-sided hand dystonia) and using only serial unilateral stimulations (e.g., the supplementary motor area cannot be studied with bilateral stimulation since stimulation of either hemisphere could contribute to the response of this midline region). We are actively pursuing such studies to define more clearly the source(s) of alteration within the basal ganglia-thalamo-cortical circuit. We are especially interested in the supplementary motor area which funnels thalamic feedback to other areas of cortex as well as contributing excitatory input into striatal matrix. If cortical grey areas are only secondarily involved ('downstream' effect), supplementary motor area activity should be increased compared with normal subjects (*see* fig. 2). On the other hand, if there are primary cortical alterations in regions such as the supplementary motor area, we would predict that its activity would be decreased. Further research will clarify these issues.

If we had limited this investigation to the evaluation of resting-state data, we would not have identified an abnormality in the sensorimotor cortex. It was necessary to use a provocative test, the vibration-induced blood flow response, to demonstrate the regional abnormality. This is not surprising from a clinical perspective since most of our patients had action-induced dystonia, and did not have apparent clinical abnormality at rest. In other words, the clinical abnormality was frequently present only when the motor system was in action, and the abnormality in sensorimotor cortex was apparent only during activation with vibration. Conceivably, similar strategies applied to other clinical conditions may help to identify abnormal regional function. This is analogous to any stress test used in clinical medicine or physiological testing.

Finally, it is important to note that our data do not support the use of the vibration-induced blood flow response as a diagnostic test for dystonia or patients at risk for development of dystonia. The experimental design of this study was not intended to address this question. While our aggregate results speak very strongly for a diminished magnitude of response to vibrotactile stimulus in sensorimotor cortex, how early this may appear or whether a diminished response, even if well-documented, necessarily predicts subsequent development of clinical symptoms is not known. Further, given the wide and overlapping range of magnitudes of response in normal controls and dystonic subjects, it would seem unlikely that this methodology could be used reliably to diagnose patients with adequate sensitivity and specificity. Similarly, clinical prognosis cannot be based upon our results. In particular, we cannot predict if a clinically uninvolved side or part of the body will become involved even if the vibration-induced blood flow response is decreased. Since most idiopathic adult-onset focal dystonias remain focal (Sheehy *et al.*, 1988), further clinical follow-up will be necessary to determine if our patient group was atypical in this regard.

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A QUANTITATIVE STUDY OF SENSORY FUNCTION IN HEREDITARY SPASTIC PARAPLEGIA

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SUMMARY

Somatic sensation was studied in 23 patients from 14 families with hereditary spastic paraplegia. Quantitative sensory testing revealed significantly raised thermal, heat pain, vibratory and tactile thresholds in patients as compared with normal controls. Cutaneous sensitivity was more severely impaired in the feet than in the hands. All patients had at least one elevated sensory threshold. Sensory nerve conduction studies were abnormal in 6 patients, 5 of whom were members of the same family. Somatosensory evoked potentials were reduced on average to half the size of those of controls. Although the clinical picture is dominated by a spastic paraparesis, subclinical sensory impairment is common in hereditary spastic paraplegia and may reflect involvement of peripheral nerves, afferent pathways in the spinal cord or both.

INTRODUCTION

Hereditary spastic paraplegia occupies a relatively unique position within the inherited neural degenerations on account of the homogeneity of its clinical picture. While associations with optic atrophy, extrapyramidal signs, amyotrophy and cerebellar ataxia have been described, these are rare. In most cases spasticity and moderate weakness of the lower limbs are the only manifestations of the disease. Reference to a sensory deficit has been made in several reports (Bickerstaff, 1950; Behan and Maia, 1974; Harding, 1981; Boustany *et al.*, 1987), but its extent has not been quantified. We have studied the incidence and severity of sensory impairment in patients with hereditary spastic paraplegia by psychophysical and neurophysiological methods. Our results show that sensory disturbance, though usually mild, is a common accompaniment of the disease.

MATERIAL AND METHODS

Patients

Twenty-three patients from 14 kinships with hereditary spastic paraplegia (HSP) were studied. The diagnosis was based on the presence of a well-documented family history and gradually progressive evolution. No sporadic cases were accepted for study. The clinical picture was dominated by a spastic paraparesis in all patients. Twelve patients were male and 11 were female. Their ages ranged from 20 to 73 (mean 45) yrs. Details are given in Table 1. Each patient's disability at the time of testing was scored in accordance with the following criteria (Behan and Maia, 1974): 1, minimal or no symptoms; 2, stiff gait but no help required to walk; 3, gait possible only with the aid of sticks or walking frame; 4, patient confined,

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TABLE 1. CLINICAL AND GENETIC DETAILS IN 23 PATIENTS WITH HEREDITARY SPASTIC PARAPLEGIA

Patient	*Age (yrs)*	*Sex*	*Kinship*	*Age at onset (yrs)*	*Severity of paraparesis*	*Additional features*
1	60	M	1	43	3	
2	32	M	1	20	2	Deafness, sensory loss, wasted EDB
3	26	F	2	2	2	
4	25	M	2	1	2	
5	58	F	3	2	2	
6	35	M	3	14	2	
7	41	F	4	11	4	
8	49	M	4	18	3	Sensory loss
9	47	F	4	8	4	Sensory loss
10	43	F	4	11	4	
11	38	F	4	7	2	Sensory loss
12	61	F	5	40	3	
13	57	F	6	30	3	
14	34	F	7	32	2	
15	73	F	7	61	3	
16	36	M	7	27	2	
17	20	M	8	9	1	
18	56	F	9	6	2	
19	65	M	10	7	3	UL amyotrophy
20	48	M	11	18	2	Sensory loss, wasted EDB
21	27	M	12	13	2	Optic atrophy
22	55	M	13	40	3	Sensory loss, wasted EDB
23	41	M	14	35	2	Sensory loss

UL = upper limb, EDB = extensor digitorum brevis muscle. For details of sensory loss, *see* text.

for practical purposes, to chair or bed. All patients gave informed consent in accordance with the Declaration of Helsinki.

Quantitative sensory examination

In all cases a detailed neurological examination was performed. This was followed by quantitative testing for temperature, pain, vibration and tactile sensory thresholds in the right hand and foot.

Thermal sensibility was tested by the Marstock method (Fruhstorfer *et al.*, 1976). The thermode employed has a stimulating surface of 2.5×5 cm which operates on the Peltier principle and can either be warmed or cooled. The temperature, measured by a thermocouple fixed to the stimulating surface, is displayed digitally and is recorded by a pen recorder. Having applied the stimulator to the skin, it was warmed at a rate of 1.0° C/s (1.5–2° C/s in the foot), starting from a baseline temperature of 31° C, until the subject first perceived warmth. At this point he pressed a switch which reversed the current and cooled the stimulator. When a sensation of cold was first felt, he again pressed the switch to reverse the current, thereby commencing a new cycle; 8–10 cycles were recorded at each site and a warm-cold threshold difference (warm-cold limen) was calculated from the latter, stable part of the recording (fig. 1). A warm-cold limen was obtained in all patients at 2 sites, namely the hypothenar eminence and the lateral aspect of the foot just below the malleolus. A weight of 240 g was placed on the upper surface of the thermode to standardize the pressure of application and obtain good contact between skin and thermode. Care was taken to ensure that the skin temperature at the onset of the procedure was 33 ± 1° C for the hand and 32 ± 1° C for the foot. The ambient temperature was 24–26° C.

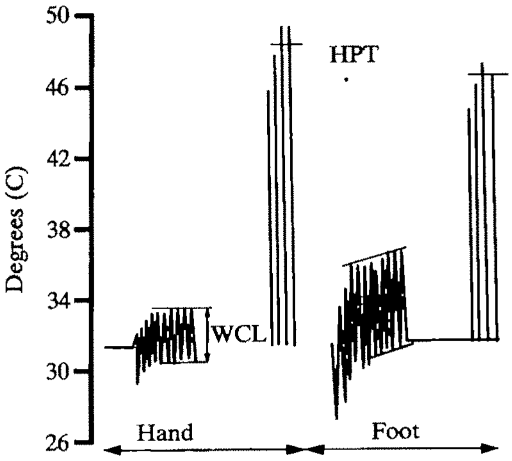

FIG. 1. Representative record of thermal (warm-cold limen, WCL) and heat pain thresholds (HPT) in the hand (*left traces*) and in the foot (*right traces*). Note rise in thresholds over the first few trials until values stabilize.

Heat pain thresholds were determined with the same equipment at the same sites on the hand and foot. The stimulating thermode was warmed at 3° C/s and the subject was instructed to press the switch when he first felt pain. The temperature was then allowed to return to baseline for 10–15 s in order to avoid nociceptor sensitization. The procedure was repeated 4 times and the mean of the last 3 values was calculated.

Vibration thresholds were obtained by means of a Vibrameter (Somedic AB), which delivers a 100 Hz sine wave through a hand-held probe. The amplitude of the sine wave was slowly increased by the operator while the displacement of the probe (in μm) was read off a continuous digital display. A pressure monitor ensured that the probe was applied with a constant force. The vibration threshold (VT) was defined as the midpoint between vibration perception and disappearance thresholds. Measurements were undertaken on the dorsum of the hand over the first metacarpal bone, on the lateral malleolus and in the area of the foot overlying the fifth metatarsal bone. At least 3 values were obtained at each site, from which a mean VT was derived.

A standard set of graded von Frey hairs was employed to assess tactile sensibility on the pulp of the index and little fingers, the hypothenar region, the lateral aspect of the foot and the pulp of the big toe. The threshold (in millinewtons, mN) was regarded as the force required to obtain a correct response in 3 out of 4 trials. Two-point discrimination was measured on the pulp of the index and little fingers and in the hypothenar region by means of calipers with blunt points and a mm scale showing the distance between the points.

Electrophysiological investigation

Nerve conduction studies were performed in 22 patients with standard techniques using a Medelec MS6 EMG system. Sensory action potentials were obtained from the right median, ulnar, superficial peroneal and sural nerves, and motor conduction velocities from the right median, ulnar, common peroneal and tibial nerves. If an abnormality was detected, the same studies were undertaken on the left side. Limb temperature was maintained at 32–34° C by means of a thermostatically-controlled infrared heat source.

Somatosensory evoked potentials were obtained bilaterally with a Cadwell 7400 4-channel recorder. The median (19 patients) and tibial (11 patients) nerves were stimulated through surface electrodes placed at the wrist and ankle, respectively. The stimulus was a rectangular electric pulse of 0.1 ms duration delivered at 5 Hz and at an intensity 25% above threshold for a visible motor twitch. During median nerve stimulation, responses were recorded at Erb's point (N9), the seventh cervical vertebra (N13) and a point on the scalp 2.5 cm behind Cz, 7 cm lateral to the midline on the contralateral side (N20). When stimulating the tibial nerve, cortical responses were obtained from the midline, 2.5 cm posterior to Cz. To ensure reproducibility 200 responses were averaged twice on each side.

Analysis of data

Results were compared with those from 124 controls of both sexes, aged 20–79 yrs, who were either healthy paramedical staff or hospital patients with nonneurological disease. Since sensory thresholds are known to increase with age (Dyck *et al.*, 1984; Kenshalo, 1986; Mitchell and Schady, 1988), control values were plotted against age and the 95% confidence limits of the regression line were calculated. Patients' thresholds were considered abnormal if they fell outside this range.

RESULTS

Genetic aspects

Inheritance was clearly autosomal dominant in 11 families, where there were affected members of both sexes in two or more generations. In kinships 2, 4 and 12, siblings were affected but there was no history of either parent having had the disease. The parents, however, were not examined. Although affected siblings may be taken as evidence of autosomal recessive inheritance, there was no parental consanguinity and autosomal dominant inheritance cannot be excluded in these families, since dominant disorders may vary in clinical expression.

The age of onset was uniformly under 20 yrs in 8 families. In the remaining 6 families the age of onset varied from 20 to 61 yrs for different family members. Using Harding's (1981) classification, 9 families were of type I (age of onset below 35 yrs), none were of type II (age of onset uniformly above 35 yrs) and 4 were mixed. In our material, therefore, a cut-off point of 20 yrs led to less overlap between families with the juvenile and adult-onset forms of hereditary spastic paraplegia than using Harding's criterion.

Clinical examination

All patients had markedly increased lower limb tone, exaggerated knee and ankle jerks and extensor plantar responses, although the severity of the syndrome varied. By disability, 3 patients had a score of 4, 7 scored 3, 12 scored 2 and 1 patient scored 1 (*see* Methods). Patients with adult-onset HSP had a similar mean disability score of 2.55 to those with juvenile onset (2.57). However, a striking difference became apparent when patients' scores were divided by the duration of disease in years. The relative disability score for patients with type I HSP was 0.082 ± 0.032, that for patients with type II HSP 0.194 ± 0.103 ($P < 0.001$). These results indicate that patients in the adult-onset group reached a given level of disability twice as fast as their juvenile-onset counterparts.

Fifteen patients had brisk upper limb reflexes without weakness. One patient (Case 19, Table 1) was unusual in that he showed prominent wasting of the muscles of his hands and forearms with depressed upper limb reflexes but no sensory loss or lower limb wasting. Another patient had perceptive deafness and a third had optic atrophy. Three patients had bilateral wasting of extensor digitorum brevis (EDB) muscles but not elsewhere. No patient had intellectual impairment, skin changes, retinal pigmentation or an extrapyramidal syndrome. Only 2 had frank pes cavus.

Seven patients, 3 of them members of the same family, had evidence of sensory impairment on standard bedside examination (Table 1). Case 2 had a 'glove and stocking' pattern of sensory loss. Case 8 had absent vibration sense to the hips. Case 9 had mild impairment of joint position sense in the toes. Case 11 showed distally reduced pin prick perception in upper and lower limbs, absent vibration sense to the pelvis and impaired joint position sense in the feet. Case 20 had impaired pin prick and light touch perception to mid-leg level. Case 22 showed loss of vibration sense and joint position sense in the feet. Case 23 had noticed numbness of his toes and was found to have impairment of pain sensitivity in the right big toe and of vibration sense below the knees. Another patient complained of unpleasant burning or 'wet' feelings in her lower limbs but had a normal sensory examination.

Nerve conduction studies

Six patients, 5 of whom were members of the same family, had frankly reduced or absent sensory action potentials in upper and lower limbs (Table 2). Despite the reduced amplitudes, there was no slowing of sensory conduction. These 6 patients were considered to have an electrophysiologically demonstrable peripheral neuropathy as well as corticospinal tract disease; 4 of them were among the 7 patients with sensory impairment on bedside examination. Motor conduction abnormalities were evident in only 3.

TABLE 2. NERVE CONDUCTION STUDIES IN PATIENTS WITH HEREDITARY SPASTIC PARAPLEGIA[1]

Case	*19*	*2*	*7*	*8*	*9*	*10*	*11*
Median MCV	Abs.	37*	60	58	60	61	55
Ulnar MCV	43*	37*	60	58	72	62	69
Common peroneal MCV	39	Abs.	50	44	46	52	43
Tibial MCV	39	–	45	43	–	35*	33*
Median SAP	6*	1.5*	Abs.	4*	2*	5*	1*
Ulnar SAP	6	–	Abs.	1.5*	3*	2*	1*
Superficial peroneal SAP	4	–	Abs.	Abs.	3*	3*	Abs.
Sural SAP	4	–	Abs.	Abs.	5	3	Abs.

[1] Only patients with at least one abnormal value (indicated by an asterisk) are given. The last 5 patients are members of the same family. MCV = motor conduction velocity ($m \cdot s^{-1}$); SAP = sensory action potential (μV); Abs. = absent.

Case 19 had impaired upper limb motor conduction and prominent electromyographic signs of denervation in forearm and hand muscles, although sensory conduction was only mildly affected. Compound muscle action potentials from EDB were reduced in 3 other patients in whom these muscles were wasted. Since motor and sensory conduction studies were otherwise normal, this isolated deficit may have been due to a local compression injury or to anterior horn cell loss and was not interpreted as a sign of polyneuropathy.

In view of the electrophysiological evidence of peripheral nerve disease in all members of kinship 4, alternative diagnoses such as adrenoleukomyeloneuropathy were considered, but adrenal function tests in an affected male were normal (including plasma ACTH, cortisol, testosterone and gonadotrophin levels and ACTH stress test).

Thermal and heat pain thresholds

The thermal threshold in the hand (expressed as the warm-cold limen) was increased in 8 patients (35%). In the foot it was raised in 17 patients (74%), the increase being of greater magnitude than in the hand (fig. 2, upper panels). Thermal thresholds were not significantly different in patients with and without an electrophysiologically demonstrable peripheral neuropathy. Of the 7 patients with clinical sensory impairment, 4 had increased thermal thresholds in the hand and 5 in the foot. There was no relationship between thermal thresholds and duration or severity of the disease.

All heat pain thresholds fell within the normal range. This is not surprising, bearing in mind that heating was not allowed to proceed beyond 50° C in order to avoid burning, and that the upper limit of normal exceeded that value for all decades. Since pain thresholds do not regress with age (Kenshalo, 1986) or do so only weakly (Mitchell and Schady, 1988), we compared heat pain thresholds in HSP patients as a group with those of controls. Values for the foot were 46.8$\pm$2.7° C (mean$\pm$SD) in patients and 44.5$\pm$3.2° C in controls ($P < 0.01$). Corresponding values in the hand were not significantly different.

Vibratory and tactile thresholds

Tactile thresholds in the index and little fingers and in the hypothenar eminence were normal in all patients. Two-point discrimination was impaired in the little finger in 3 patients and on the hypothenar eminence in 6. In the foot, tactile thresholds were elevated in 10 out of 20 patients, including 4 with a peripheral neuropathy, 3 of whom had been found to have sensory impairment in bedside testing (fig. 2, middle panels).

Vibration thresholds in the hand were elevated in only 1 patient. In the foot, however, vibration thresholds were abnormally high in 13 out of 20 patients (65%), including all patients with an electrophysiologically demonstrable polyneuropathy (fig. 2, lower panels). Vibration thresholds were also obtained from the ankle with similar results; 53% of patients had elevated thresholds at this site. Ten out of 17 patients without neuropathy had impaired vibratory perception in the foot and/or at the ankle. There was no correlation between tactile or vibratory thresholds and duration of disease, age of onset, severity of disease or thermal thresholds.

All patients had at least one abnormal sensory threshold. Since only 7 had clinical sensory impairment, it follows that an unsuspected sensory deficit was found in 70% of patients. Three or more raised thresholds were found in 13 patients, of whom 12

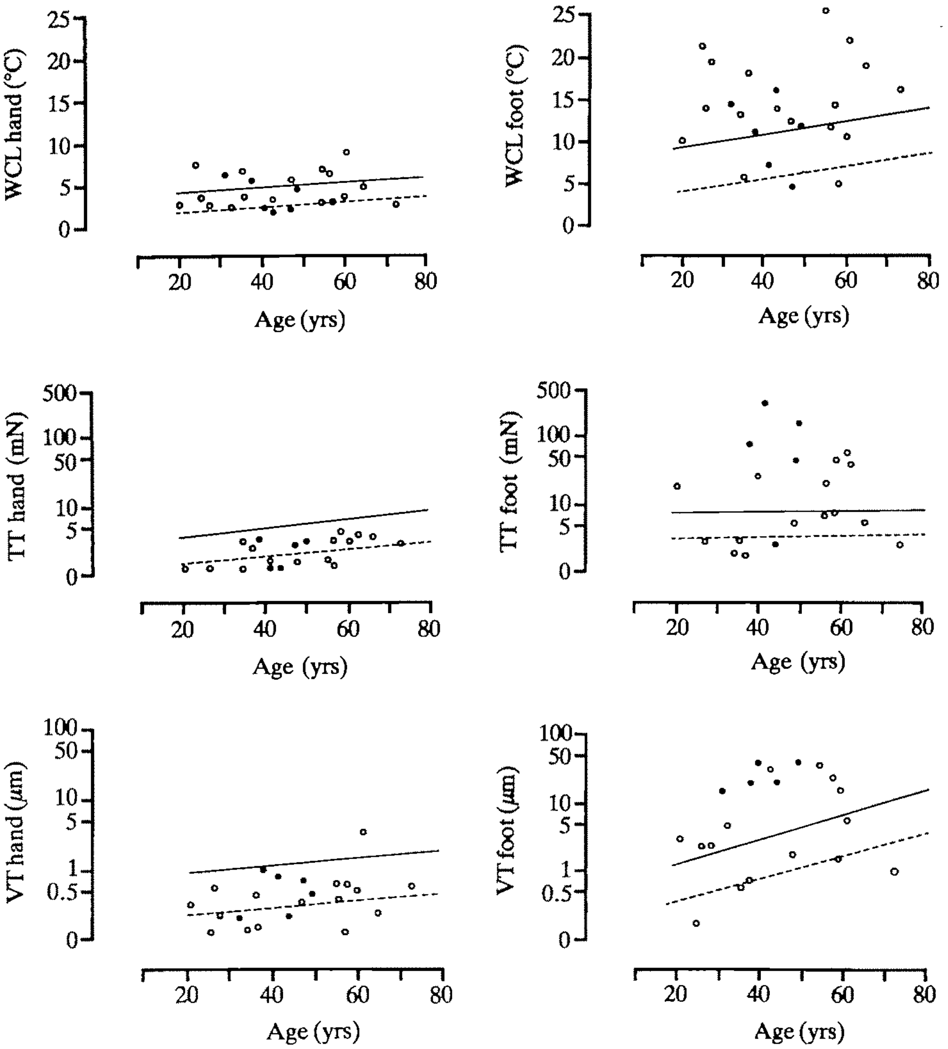

FIG. 2. Warm-cold limen (WCL), tactile threshold (TT) and vibration threshold (VT) plotted against age (in yrs) in patients with hereditary spastic paraplegia. *Left panels* correspond to the hand, *right panels* to the foot. Filled circles represent patients with a peripheral neuropathy. The least squares regression line (broken) and upper 95% confidence limit (solid line) for 124 normal controls are also shown. Note log scale for the ordinate in the lower four panels.

had involvement of sensory submodalities mediated by both large fibres (touch, vibration) and small fibres (warm, cold). With a simplified protocol relying on the thermal and vibratory thresholds at a single site in the foot, 19 patients would have been found to have impaired sensibility.

Somatosensory evoked potentials

Somatosensory evoked potentials (SEPs) to median nerve stimulation could be obtained in 17 out of 19 patients. Both patients with absent SEPs also had reduced peripheral sensory action potentials. Three patients had a delayed N9 peak recorded over the brachial plexus, one had a prolonged N9–N13 interpeak latency difference and 2 had prolonged N13–N20 interpeak latencies. In all these cases the delay was modest, amounting to less than 2 ms outside the normal range. After excluding patients with a neuropathy, the amplitude of subcortical SEPs, both at the brachial plexus and over the cervical cord, did not differ significantly from that of normal controls. However, the amplitude of cortical SEPs was significantly reduced. In 14 patients with normal peripheral sensory conduction, the mean N20 potential amplitude was $2.8 \pm 1.1\ \mu V$, compared with $3.8 \pm 2.0\ \mu V$ in control subjects ($P < 0.02$).

Somatosensory evoked responses to tibial nerve stimulation were recorded in 10 patients without evidence of peripheral neuropathy. In 1 case they were absent bilaterally, while in 4 cases they were absent unilaterally but could be obtained from the other side. The mean amplitude of the P40 potential, when recordable, was $2.4 \pm 0.8\ \mu V$ in patients and $5.3 \pm 2.1\ \mu V$ in control subjects ($P < 0.001$). The latency of the P40 peak was normal in all cases. Fourteen patients (60%) had an abnormality of either nerve conduction studies, somatosensory evoked potentials or both.

DISCUSSION

Hereditary spastic paraplegia (HSP) presents a relatively uniform clinical picture in the majority of patients. In the uncomplicated form there is insidiously progressive lower limb spasticity, with moderate weakness and no lower motor neuron features. The disease may be transmitted as an autosomal dominant or, less commonly, as an autosomal recessive trait. This distinction is not always easy, as dominant disorders may show variable clinical expression. A family in point is our kinship 4, where all of 6 siblings had the disease, and neither parent was known to have been affected. Either autosomal dominant or autosomal recessive inheritance is possible. Inheritance may have been recessive in 2 other families (kinships 2 and 12), but there was no consanguinity and the parents were not examined, so autosomal dominant transmission again cannot be excluded. Since only patients with a clear family history were admitted to the study, there may be an over-representation of dominantly inherited kinships in our material.

Subdivision of patients is possible on the basis of age of onset of symptoms. In a study of 22 families, Harding (1981) divided dominant HSP into two forms, namely type I, with an age of onset below 35 yrs, and type II, with onset usually over 35 yrs. In our families, 20 yrs was a better cut-off point between juvenile and adult-onset forms of HSP. By this criterion, 8 families were uniformly of juvenile onset and 6 families were of adult onset. On average, within the limitations imposed by our rather crude disability scoring system, the latter progressed twice as rapidly as the former. Harding (1981) also found that late onset is associated with a worse prognosis.

Families have been reported in which HSP is associated with optic atrophy, extrapyramidal disease, deafness, amyotrophy or cerebellar ataxia (for review, *see* Harding, 1984). Twenty of our 23 patients had the so-called 'pure' form of the disease. One patient had upper limb amyotrophy as well as a paraparesis, a previously recognized association (Silver, 1966). Another patient had perceptive deafness and a third had optic atrophy. In the presence of an otherwise typical clinical picture and a positive family history, their inclusion in the series was thought justified. Six patients had reduced or absent peripheral sensory action potentials, implying that they had a polyneuropathy as well as corticospinal tract disease. None of them was similar to previously described cases of hereditary spastic paraparesis with sensory neuropathy, who suffered from a progressive ulcerating sensory polyneuropathy which overshadowed the pyramidal syndrome (van Epps and Kerr, 1940; Khalifeh and Zellweger, 1963; Koenig and Spiro, 1970; Cavanagh *et al.*, 1979). The clinical picture in our patients was also quite unlike that of families with peroneal muscular atrophy with pyramidal features (Harding and Thomas, 1984), in whom the neuropathy predominates. Adrenoleukomyeloneuropathy was considered in kinship 4 but was thought to be unlikely by the demonstration of normal adrenal function tests in a male member of the family.

Other authors have reported impaired sensation in some patients with otherwise uncomplicated HSP. Bickerstaff (1950) found defective lower limb sensitivity to vibration in 7 out of 43 examined members of a large kinship with HSP. In no case was any superficial sensory loss discovered. In 52% of the cases reported by Behan and Maia (1974), 27% of those of Harding (1981) and 60% of those of Boustany *et al.* (1987) there was a sensory deficit in the lower limbs. It was restricted to vibration sense and, in a few patients, joint position sense. Seven of our patients had sensory impairment on bedside testing, predominantly involving dorsal column submodalities, as in previous reports, though 4 patients had reduced pin prick perception, which in 1 case extended to the upper limbs. Four of these 7 patients were among the group in whom nerve impairment studies showed a peripheral neuropathy.

Quantitative sensory testing (QST) was more revealing than bedside examination of sensibility. Our results show that some sensory abnormality is almost universal in the lower extremities of patients with HSP if sensitive enough methods are applied to detect it. QST is often considered excessively cumbersome for routine use, but our battery of tests at several sites in the hand and foot usually took no more than 45 min to apply. It allowed us to test a range of sensory submodalities, an evident advantage in view of the variability inherent in any form of sensory testing and the lack of correlation between the various thresholds. With a simplified protocol, relying on results obtained at a single site in hand and foot, QST need be no more time-consuming than standard electrophysiological tests, and yet our findings suggest that in some instances it may be more sensitive. While only 60% of our patients had abnormal nerve conduction studies and/or somatosensory evoked potentials, all had one or more abnormal sensory thresholds.

The methodology of QST requires further discussion. For the sake of simplicity we chose the method of limits for measurement of cutaneous thresholds. Forced-choice techniques are psychophysically superior, since they reduce response bias and eliminate variability in reaction times (Dyck *et al.*, 1984; Jamal *et al.*, 1985), but they also lengthen the procedure. This is particularly important when several sensory submodalities need to be tested, as distractability will increase with fatigue. For thermal thresholds, the intrasubject variability inherent in the 'Marstock' technique presents a serious problem in longitudinal studies (Fagius and Wahren, 1981), but it should not invalidate the results of case control studies such as ours. The Marstock method has the added advantage of allowing measurement of pain thresholds (Fruhstorfer *et al.*, 1976). With regard to vibration sense, the vibrameter that we employed has a pressure monitor which ensures that the probe is applied with a constant force, contrary to the standard biothesiometer which does not make allowances for variable damping of the vibratory stimulus (Goldberg and Lindblom, 1979). Lastly, we chose von Frey hairs to assess tactile sensitivity because, although they do not provide a fully controlled physical stimulus, they are cheap and produce a similar range of thresholds in fingers and toes to those obtained with more sophisticated techniques (Dyck *et al.*, 1984). It should be emphasized that the methods used, and the testing sequence, were the same in patients and controls.

The disturbance of cutaneous sensitivity detectable by QST affected all modalities. Most surprising was the increase in thermal thresholds in patients as compared with controls, especially in the lower limbs, where raised values were found in three-quarters of the patients. Heat pain thresholds in the foot were also increased, although less strikingly. This disturbance of 'spinothalamic' function applied regardless of whether patients with an electrophysiologically proven sensory polyneuropathy were excluded. There was no correlation between sensory thresholds and disease severity, disease duration or age of the patient. Our results, therefore, do not support the view expressed by some authors that sensory loss in HSP is increasingly common with advancing age (Schwarz and Liu, 1956; Behan and Maia, 1974).

All previous reports of clinical sensory impairment in uncomplicated HSP refer to modalities mediated by large fibres. Our finding of abnormal vibratory and tactile thresholds was therefore less unexpected than the results of thermal testing. Although patients with a polyneuropathy had the highest thresholds, vibration perception was impaired in the foot or at the ankle in over half of those without a neuropathy. This suggests central nervous system dysfunction, a conclusion further supported by the SEP results. After excluding patients with abnormal peripheral conduction, the amplitude of cortical SEPs from the lower limbs was less than half that of healthy controls. Cortical SEPs from the upper limbs were also significantly reduced, though to a lesser extent. Abnormalities in somatosensory evoked potentials in HSP have previously been reported by other authors (Pedersen and Trojaborg, 1981; Thomas *et al.*, 1981; Dimitrijevic *et al.*, 1982).

Neuropathological studies have shown dorsal column degeneration in some patients with HSP (Schwarz and Liu, 1956; Behan and Maia, 1974), in keeping with the neurophysiological evidence of posterior column dysfunction. By contrast, there are no reports of spinothalamic tract degeneration in HSP. Nonetheless, our data indicate that afferent pathways mediating pain and thermal sensibility are not spared. There are pointers to both peripheral and central nervous system disease. Six of our patients clearly had a neuropathy. The others might be argued to have had a small fibre neuropathy, since nerve conduction studies assess function in large myelinated fibres only. On the other hand, some of the highest thermal thresholds correspond to patients with normal peripheral conduction, suggesting spinothalamic tract involvement in some cases.

Whatever the precise site of damage, the disease may extend to the upper limbs in a few patients, as evidenced by abnormal sensory thresholds or exaggerated tendon reflexes.

It is interesting that 5 out of the 6 patients with a neuropathy were members of the same family. This may explain why the proportion of patients with neuropathy in our series is greater than that of previous authors. A number of reports of HSP with normal peripheral nerve function concern single families (Holmes and Shaywitz, 1977; Dimitrijevic *et al.*, 1982) or only 3 families in the study by McLeod *et al.* (1977). If neuropathy does not occur randomly in HSP but within genetically distinct subgroups, it is unlikely to be recognized unless large numbers of families are studied. We wish to emphasize, however, that even in the absence of a polyneuropathy sensory impairment is common in HSP, pointing to the kind of multisystem involvement that is associated with most familial nervous system degenerations.

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FAMILIAL CEREBRAL AMYLOID ANGIOPATHY WITH NONNEURITIC AMYLOID PLAQUE FORMATION

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SUMMARY

Two families have been described previously with the features of an autosomal dominant familial cerebral amyloid angiopathy with nonneuritic plaque formation. The clinical features of the cases were dementia, spastic paralysis and ataxia. It has now been established that both families were descended from a common ancestor and the case histories of 26 affected individuals in 5 generations of this pedigree are reported. An autopsy study has been performed on a recent case. The findings are described and compared with the four previously published autopsy studies in this family, which is then discussed in the context of recent advances in the nosology of familial disorders in which cerebral amyloid angiopathy and other forms of cerebral amyloid deposition occur.

INTRODUCTION

Worster-Drought *et al.* (1933) first reported a family with an autosomal dominant condition characterized clinically by the onset in the fifth decade of dementia, progressive spastic tetraparesis and cerebellar ataxia. Subsequently the autopsy findings were described in two siblings (Worster-Drought *et al.*, 1940, 1944). These papers have been extensively quoted and are of particular interest because the pathological findings constitute the earliest English language descriptions of cerebral amyloid (congophilic) angiopathy (CAA). The appearances were described in the original papers as a form of hyaline degeneration of the blood vessels and it was not until some years later (McMenemey, 1952, 1970) that the pathological material was reviewed and the fact that the material had the staining properties of amyloid was appreciated. The classification of this family has remained uncertain (Baraitser, 1982) and it has been quoted as an example of atypical Alzheimer's disease (Corsellis and Brierley, 1954; Boellaard and Schlote, 1980; Aikawa *et al.*, 1985); an example of the Gerstmann-Sträussler syndrome (GSS) (Masters *et al.*, 1981*a*; Keohane *et al.*, 1985; de Courten-Myers and Mandybur, 1987; Pearlman *et al.*, 1988); and has also been likened to other familial amyloid angiopathies usually associated with intracranial haemorrhage and thus regarded as a specific form of primary CAA (Gudmundsson *et al.*, 1972; Shaw, 1979; Pro *et al.*, 1980; Vinters, 1987).

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Griffiths *et al.* (1982) have recently described autopsy findings in two siblings who had died from an illness which the authors suggested was 'clearly the same' as that reported by Worster-Drought *et al.* (1940, 1944). They were able to identify very few other cases that truly resembled the 2 siblings in a thorough survey of the literature. The purpose of this paper is to report genealogical evidence which has shown that the 2 'families' are descended from a common progenitor: the clinical details of 26 affected members in 5 generations of this pedigree are now available, together with pathological findings in a newly autopsied case. The disorder is then discussed in the light of the considerable recent advances in the understanding of familial CAA and other syndromes involving amyloid deposition in the central nervous system. Some of the findings have been published in abstract form (Plant and Révész, 1989).

PATIENTS AND METHODS

Family study

Reliable information has been assembled concerning 26 affected family members. The detailed clinical histories are given in the Appendix, together with their sources.

Postmortem examination

A postmortem examination was carried out on a further affected family member (Case V41 in fig. 1 and Appendix) and the findings have been compared with the results obtained in 4 previously published cases (IV13, IV15, Worster-Drought *et al.*, 1940, 1944; V4, V7, Griffiths *et al.*, 1982) and 1 recently deceased unpublished case (V45, material provided by courtesy of P. L. McGeer). Postmortem examination was carried out 24 h after death. The right half of the brain, including brainstem and cerebellum and also parts of the lower cervical and thoracic spinal cord, were immersed and fixed in 10% buffered formalin while the left half was deep frozen and kept for further neurochemical studies. The right half of the brain was cut in coronal slices after 3 wks of fixation. Several representative blocks were taken and these were embedded in paraffin-wax and celloidin. Sections of 20 μm thickness were cut from the celloidin blocks, and 7–10 μm thick sections from those embedded in paraffin-wax. These were stained with haematoxylin and eosin, Klüver-Barrera luxol fast blue and cresyl violet, modified Bielschowsky silver, periodic acid-Schiff (PAS) and haematoxylin, Mallory phosphotungstic acid haematoxylin (PTAH), Heidenhain myelin, Congo red and thioflavin T. Sections (7 μm) of paraffin-wax embedded blocks were used for the immunohistochemical demonstration of glial fibrillary acidic protein (GFAP). One block of the parietal area was cut serially in order to establish vascular changes in connection with a cystic infarct (lacune). The frequency of perivascular and other amyloid plaque-like deposits in different areas of cerebral cortex and subcortical white matter was estimated in a semiquantitative way using 10 μm PAS-stained sections. Amyloid plaques were counted in 25 consecutive fields of each gyrus from neocortical areas investigated at ×100 magnification, and were also counted in different areas of the hippocampal formation over 1 to 3 fields. The results were then averaged to provide single plaque counts for 1 mm^2 area of each anatomical region. The frontal and parieto-occipital plaque counts were compared with the help of Mann-Whitney U test.

Several pieces of cerebral cortex, hippocampus, cerebellum, fixed originally in formalin, were washed in phosphate buffer, postfixed in 1% buffered osmium tetroxide, dehydrated in ethanol and embedded in Araldite. Semithin and ultrathin sections were cut and the ultrathin sections examined in a Siemens Elmiskop I electron microscope after double staining with uranyl acetate and lead citrate.

RESULTS

Family study

The pedigree is shown in fig. 1 to illustrate the transmission of the gene in this family. Apart from bringing the pedigree up to date, genealogical analysis has permitted us to combine 2 previously published pedigrees. In the pedigree published by Worster-Drought *et al.* (1940), Case 7 (III1 in fig. 1) was recorded as unaffected although it was known that a daughter had died in an asylum. This pedigree had been compiled from information provided by the husband of IV15 at a time when she was demented. However, in the National Hospital case notes of IV12 (admitted twice, in 1924 and 1926), a family history given by IV15 at a time when she was unaffected by the disease clearly states that III1 had died of the family disease. Furthermore, details such as the married name of III1 and the occupation of her husband have proved that the grandmother of the siblings reported by Griffiths *et al.* (1982; 'A' in the published family tree) was also our Case III1. Further research has provided a more detailed account of the descendants of III1 than was available to Griffiths *et al.* (1982).

The main symptoms of the illness in the affected members are given in Table 1 (*see* Appendix for detailed case histories). The mean age of onset of symptoms has been 47 (range 40–57) yrs and the mean age at death 56 (range 50–66) yrs. All cases have in the late stages of the illness manifested a chronic vegetative state; they were mute and unresponsive, doubly incontinent with severe spasticity and often contractures.

In all cases dementia and spasticity have been prominent clinical features. Memory impairment has been the earliest manifestation of the dementia. In the case of V41 a psychometric assessment was carried out at an early stage in the disease (she had had symptoms for 1 yr): verbal IQ was well preserved at 115 but there was marked impairment of memory with milder impairment on perceptual tests. Similar results were obtained in V2 3 yrs following the onset of symptoms. Cerebellar signs have been a common feature. Some affected individuals have sustained stroke-like episodes but there have been no instances of massive intracranial haemorrhage except in V40, who was found at autopsy to have a ruptured berry aneurysm. The brain was not examined in detail and it is likely that this was a coincidental aneurysm. In view of the facts that he had no symptoms before the subarachnoid haemorrhage and was aged only 48 yrs at death there is no way of knowing whether or not he was affected by the disease unless either of his 2 sons begin to show signs of it.

Less constant clinical features have been headaches, personality change and 'blackouts'. Two cases have been found to have depressed tendon reflexes despite spasticity and 1 of these 2 had myoclonus. It is possible that the clinical course has been modified in those cases known to have had coexisting hypertension (V2, V4, V45), all of whom suffered stroke-like episodes.

The autosomal dominant mode of inheritance has been confirmed by the continued uninterrupted transmission from one generation to the next and the segregation and sex ratios (Table 2). In this analysis, in the absence of autopsy information, it has been

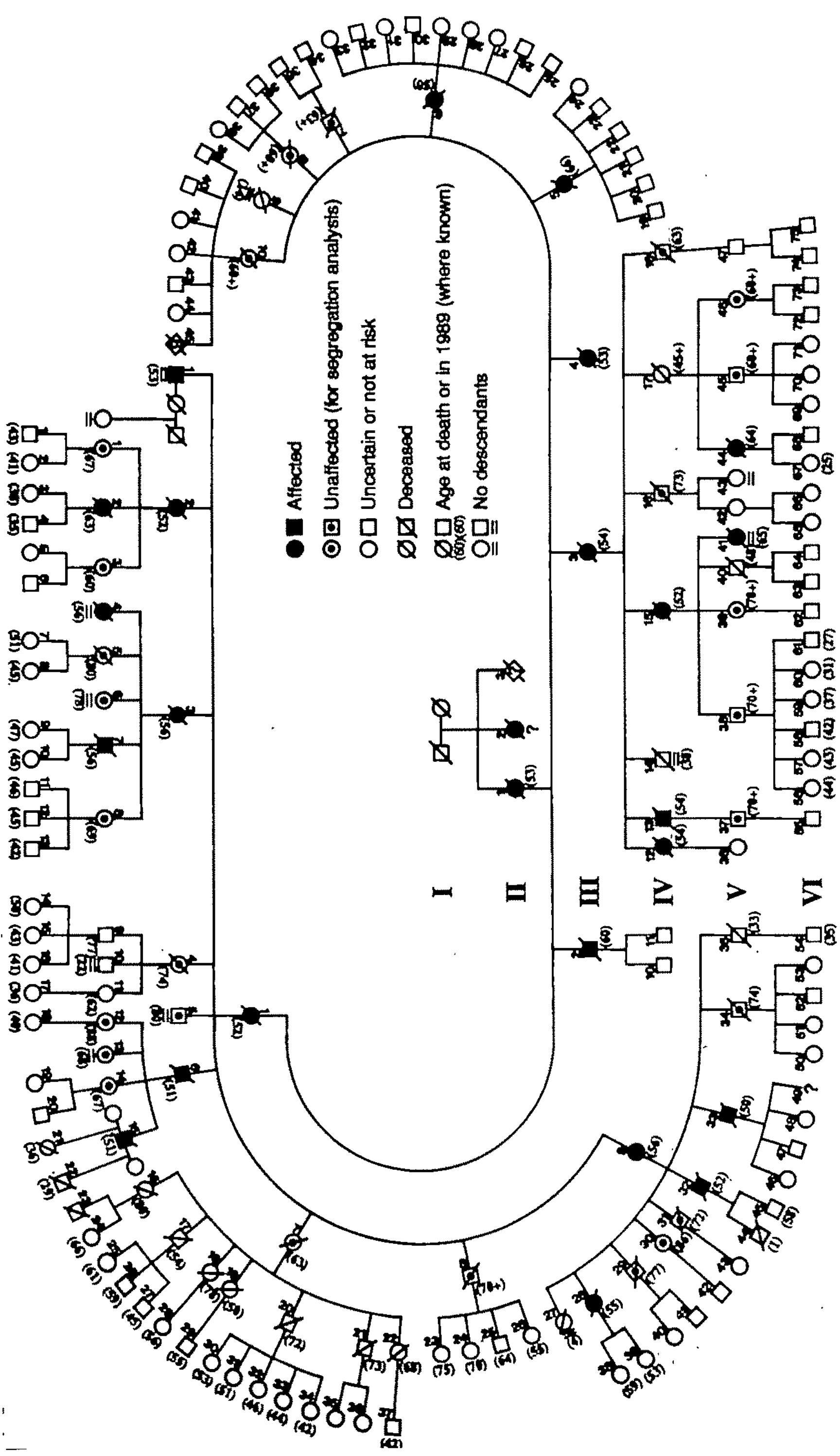
● ■ Affected
⊙ ▣ Unaffected (for segregation analysis)
○ □ Uncertain or not at risk
Deceased
(60) Age at death or in 1989 (where known)
No descendants
I
II
III
IV
V
VI

FIG. 1. Pedigree.

TABLE 1. CLINICAL FEATURES OF THE DISORDER IN AFFECTED FAMILY MEMBERS SHOWN IN FIG 1

Case	*Sex*	*Age at onset of symptoms (yrs)*	*Age at death (yrs)*	*Personality changes (irritability depression)*	*Progressive memory loss*	*Progressive paralysis*	*Spasticity*	*Progressive cerebellar ataxia dysarthria*	*Brainstem symptoms (diplopia, giddiness, bulbar palsy)*	*Headaches*	*Stroke-like episodes*	*Additional features*
II1	F	40	53		+	+	+	0	0	0	+	
II2	F											
III1	F		52	+	+	+	+	0	0	0	0	
III2	M	57	60		+	+*	+	0	0	0	0	
III3	F	44	54		+	+*	+	+	+	0	+	
III4	F	48	53		+*	+	+	0	0	0	0	
III5	F	48	66		±	+*	+	0	+	0	0	
III6	F	48	50		0	+	+	0	0	0	0	
IV1	M	40+	53		+	+	+	+*		0	0	
IV2	F	42	52		+	+	+	0	+*	+*	0	
IV3	F	46	56		+	+*	+	0	0	+	0	
IV6	M	45	51	+	+*	+	+	+	0	+	0	
IV9	F	50	56								+	
IV12	F	44	54		+	+*	+	+	+	0	+	
IV13	M	46	54	+	+*	+	+	+	+	0	0	
IV15	F	44	56	+*	+	+	+	+	+	0	0	
IV17	F	43		+	+*	+	+	+	0	0	0	
V2	F	57	63	+	+	0	+	+*	+	+	+*	Areflexia, unreactive pupils, 'blackouts', hypertension
V4	F	54	61	0	+	+	+	+*	0	0	+	'Blackout', hypertension
V7	M	50	56	0	+*	+	+	+*	0	0	0	Kyphoscoliosis from his teens
V15	M	45	51	0	+	+		+*	+	0	0	
V28	F	50	55	+	+	+	+	+		0	+*	
V32	M		52									
V33	M	48	50			+*	+					
V41	F	56	65	0	+*	+		+*	+*	0	0	
V45	F	42	64	0	+*	+	+	0	+	0	+	'Blackouts', hypertension, diminished tendon reflexes

+ = definitely present; ± = definitely present, but to a minor degree; 0 = definitely absent; blank = insufficient information; * = earliest manifestation.

TABLE 2. GENETIC ANALYSIS OF THE PEDIGREE DATA, SEGREGATION AND SEX RATIOS*

Sibs	*Female*	*Male*	*Total*
Affected	16	8	24
Unaffected	15	11	26
	31	19	50

Segregation ratio	24/50 = 48%	($P > 0.05$)
Sex ratio (affected)	8/24 = 33.3% male	($P > 0.05$)
Sex ratio (unaffected)	11/26 = 42.3% male	($P > 0.05$)

* In this analysis it has been assumed that any individuals who have reached the age of 60 yrs without showing evidence of the disease were unaffected. Siblings who have died before reaching age 60 of an unrelated cause have been excluded. There is a preponderance of females in this group and the low proportion of affected males is not statistically significant (χ^2 test with Yates correction).

assumed that individuals who have reached the age of 60 yrs without symptoms did not have the disease.

CT and MRI scan appearances

Fig. 2 shows a CT brain scan of Case V41, 1 yr following the onset of her symptoms at the age of 58 yrs, showing mild ventricular dilatation and excess low attenuation in frontal and parietal white matter. These appearances are more clearly demonstrated in the MRI scan shown in fig. 3 which was carried out on V2 at age 60, 3 yrs following the onset of symptoms. These images show abnormal periventricular white matter with U fibre sparing, a relatively normal appearance of the basal ganglia and no cortical atrophy. Abnormal areas of high signal are also seen in the brainstem and white matter of the cerebellar hemispheres.

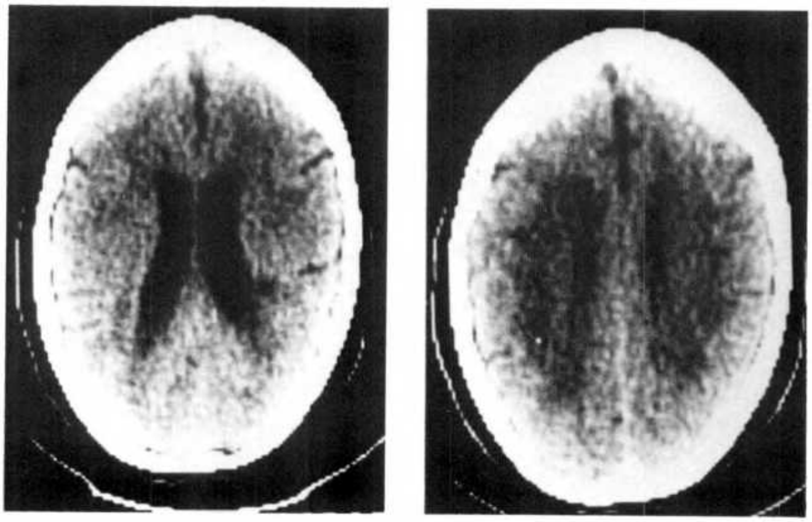

FIG. 2. *Case V41*. CT brain scan performed 1 yr following the onset of symptoms at age of 58 showing white matter changes.

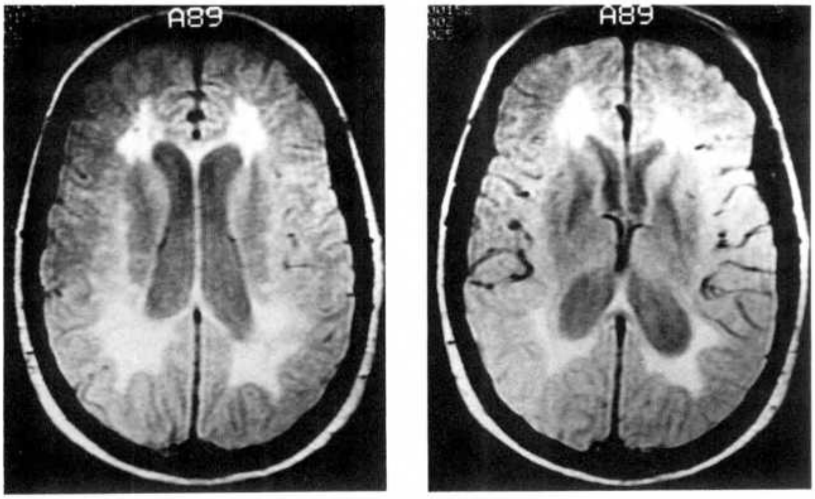

FIG. 3. *Case V2*. MRI brain scan at age of 60 yrs, 3 yrs following onset of symptoms, showing extensive periventricular white matter changes.

Pathological findings (Case V41)

The immediate cause of death was bilateral bronchopneumonia. The coronary arteries, and the thoracic and abdominal aorta showed minimal atherosclerosis. The unfixed brain weighed 1400 g. There were no relevant findings, and especially no amyloid, on microscopic examination of extraneural tissues.

The right half of the brain weighed 650 g after fixation. The leptomeninges were slightly thickened over the frontal and central gyri. The hemisphere sulci were slightly widened and the cerebellum seemed to be moderately, but diffusely, atrophied. The cerebral cortex appeared to be well preserved throughout. In the deep periventricular white matter and corona radiata there were several small cystic infarcts. The most affected parietal and occipital white matter was greyish in colour and the surface was finely granular (fig. 4). In addition, the deep white matter was considerably atrophied and all parts of the lateral ventricle were enlarged. With the exception of the anterior third of the corpus callosum, which was relatively well preserved, this structure appeared significantly shrunken. The brainstem and the lower cervical and thoracic spinal cord, the only segment of the spinal cord received for investigation, were normal.

Histological findings

The pathological changes are summarized in Table 3 and a detailed description is given below. The main histological findings were of severe and widespread deposition of amyloid in small cerebral arteries and arterioles; the presence of amyloid plaques of different types; the presence of neurofibrillary tangles (NFTs); and ischaemic white matter damage.

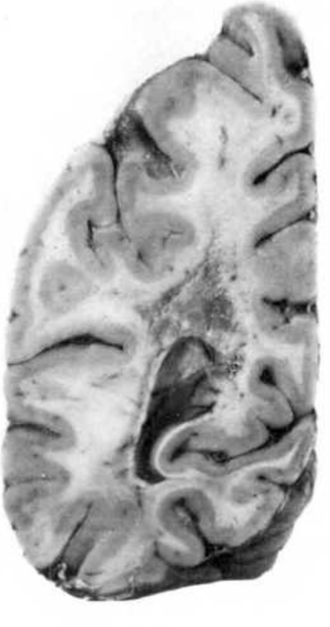

FIG. 4. *Case V41.* Parieto-occipito-temporal brain slice showing grey discolouration of periventricular white matter.

TABLE 3. TOPOGRAPHICAL DISTRIBUTION OF MAIN PATHOLOGICAL FINDINGS

	Amyloid plaques								
Area investigated	*LGP*	*SMP*	*PVP*	*NP*	*NFTs*	*Vascular amyloid*	*Neuron loss*	*Gliosis*	*Myelin pallor*
Frontal cortex	–	–	+	–	–	+	–	Subpial	–
Parietal cortex	+	–	+	–	–	+	–	Subpial	–
Temporal cortex	+	–	+	–	–	+	–	Subpial	–
Occipital cortex	+	–	+	–	–	+	–	Subpial	–
Hippocampus	+	+	+	+	+	+	+	+	–
Amygdala	+	+	+	+	+	+	+	+	–
Cerebral white matter	+	–	+	–	–	+	–	+	+
N. basalis Meynert	–	–	+	–	+	+	–	–	–
Striatum	–	–	–	–	–	+	–	–	–
Pallidum	–	–	–	–	–	+	–	–	–
Thalamus	–	–	–	–	–	+	+	+	–
Subthalamic nucleus	–	–	–	–	–	+	–	–	–
Red nucleus	–	–	+	–	–	+	–	–	–
Substantia nigra	–	–	–	–	–	+	–	–	–
Mesencephalon	+	–	–	–	–	+	–	–	–
Pontine raphe	–	–	+	–	+	+	–	+	–
Inferior olive	+	–	+	–	–	+	+	+	+
Medullary pyramids	–	–	–	–	–	+	–	+	+
Restiform body	–	–	–	–	–	+	–	+	+
Spinal cord	+	–	+	–	–	+	+	–	+
Cerebellar cortex	+	–	+	–	–	+	+	+	–
Cerebellar white matter	–	–	+	–	–	+	–	+	+
Dentate nucleus	–	–	+	–	–	+	+	+	+

LGP = large plaques; SMP = small plaques; PVP = perivascular plaques; NP = neuritic plaques; NFTs = neurofibrillary tangles; + = pathological change found; – = pathological change not found.

Blood vessels

The main trunks of cerebral arteries in the meninges showed only rare intimal thickening and atherosclerotic changes. However, the small arteries and arterioles of the generally thickened leptomeninges, cerebral and cerebellar cortices and white matter, basal ganglia, diencephalon, brainstem and spinal cord all exhibited severe generalized deposition of PAS and Congo red positive material. This was birefringent, with the characteristic apple-green colour in polarized light after Congo red staining, and was fluorescent in thioflavin T preparations, thus confirming the presence of amyloid (fig. 5A). The diameter of the vessels affected by amyloid deposition was never larger than 150 μm. Capillaries in the parietal and occipital cortex, cerebral white matter, cerebellar cortex, brainstem and spinal cord were frequently involved. Amyloid did not appear to be present in veins.

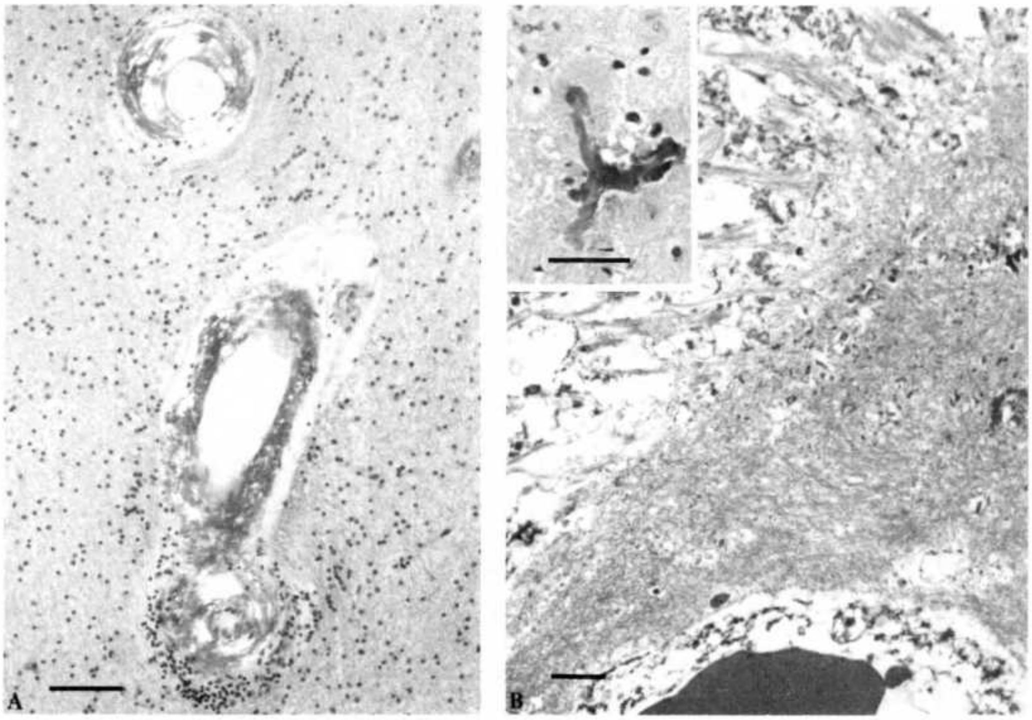

FIG. 5. A, arteriolar thickening with deposition of amyloid showing birefringence. Congo red, polarized light. Bar = 100 μm. B, electron micrograph of an arteriole showing a thickened wall composed of fibrillary structure with radiating fibrils. Bar = 0.5 μm. *Insert*: cortical capillary with amyloid. PAS stain. Bar = 50 μm.

Different stages of amyloid deposition resulted in different types of degenerative changes. (1) Severe homogeneous thickening of the arteriolar wall resulting in narrowing or complete obstruction of the lumen. This change was most often found in the cerebral white matter. Thickening of capillary walls also resulted in narrowing of lumina and occasionally complete obliteration (fig. 5B). (2) Frequent fibrous intimal thickening with an 'onion skin' appearance, and fragmentation of the internal elastic lamina and significant narrowing of the lumen, associated with amyloid. (3) Splitting of the arteriolar wall producing the picture of 'double barrelling', observed most frequently in the wall of the leptomeningeal, cortical and white matter arterioles. (4) Occasional perivascular and rare transmural inflammatory infiltrates composed mainly of lymphocytes were seen. In a few instances plasma cells and multinucleated histiocytic cells were also present. (5) Thinning of the degenerate arteriolar wall with occasional aneurysmal formation was also a feature. (6) Spicules of amyloid frequently spread radially from capillaries into perivascular neural tissue, to produce perivascular plaques (drusige Entartung; Scholz, 1938). These were seen in many areas of the cerebral hemispheres, brainstem, cerebellum and spinal cord (*see* below).

Plaque formation

'Large' plaques. These plaques (approximate maximum diameter: 150 μm) appeared as large globular masses, often with a central, strongly congophilic star-shaped core and peripheral radiating fine spicules or coarser processes. The outermost part of these plaques was always composed of a finely fibrillated pale, congophilic area (fig. 6A). Some of the cortical plaques were similar to Kuru plaques (*see*, e.g., Boellaard and Schlote, 1980; Schlote *et al.*, 1980). There were occasional microglial cells inside or near these plaques. With PTAH and GFAP stains a fine network of glial fibres was revealed around the outside of the large plaques, and delicate glial fibres appeared to spread into the centre from the periphery (fig. 6B). These plaques were most numerous in the fascia dentata, CA3 and CA4 segments of the hippocampal pyramidal cell layer, presubiculum, and basolateral nucleus of the amygdala. They were occasionally seen in the cerebellar cortex, cerebral cortex, subcortical white matter, brainstem and spinal cord (fig. 6C and D).

'Small' plaques. These plaques (maximum diameter around 30 μm) closely resembled the central core of the large plaques, but were naked and did not show any peripheral pale zone. They were made up of a more or less homogeneous central area from which either fine peripheral spicules or coarser, irregular processes radiated. Many of these small plaques had irregular outlines. The small plaques also gave positive reactions for amyloid (fig. 7A). They were numerous in the CA1 and, in part, CA2 segments of the hippocampal pyramidal cell layer (fig. 7B). Similar small plaques were only occasionally seen in the granular cell layer of the cerebellum and also the basolateral subnucleus of the amygdala. An interesting pattern of distribution of plaques was noted in the hippocampus. The small plaques were found in CA1 and CA2, while the large ones were restricted to CA3, CA4, the granular cell layer of the fascia dentata and prosubiculum. In CA1 only occasional neurons were seen, while the number of remaining neurons in CA2, CA3, CA4 and prosubiculum was slightly higher.

'Perivascular' plaques. These plaques appeared as pale, homogeneous or fibrillated structures around capillaries or arterioles. They were faintly PAS positive, but not

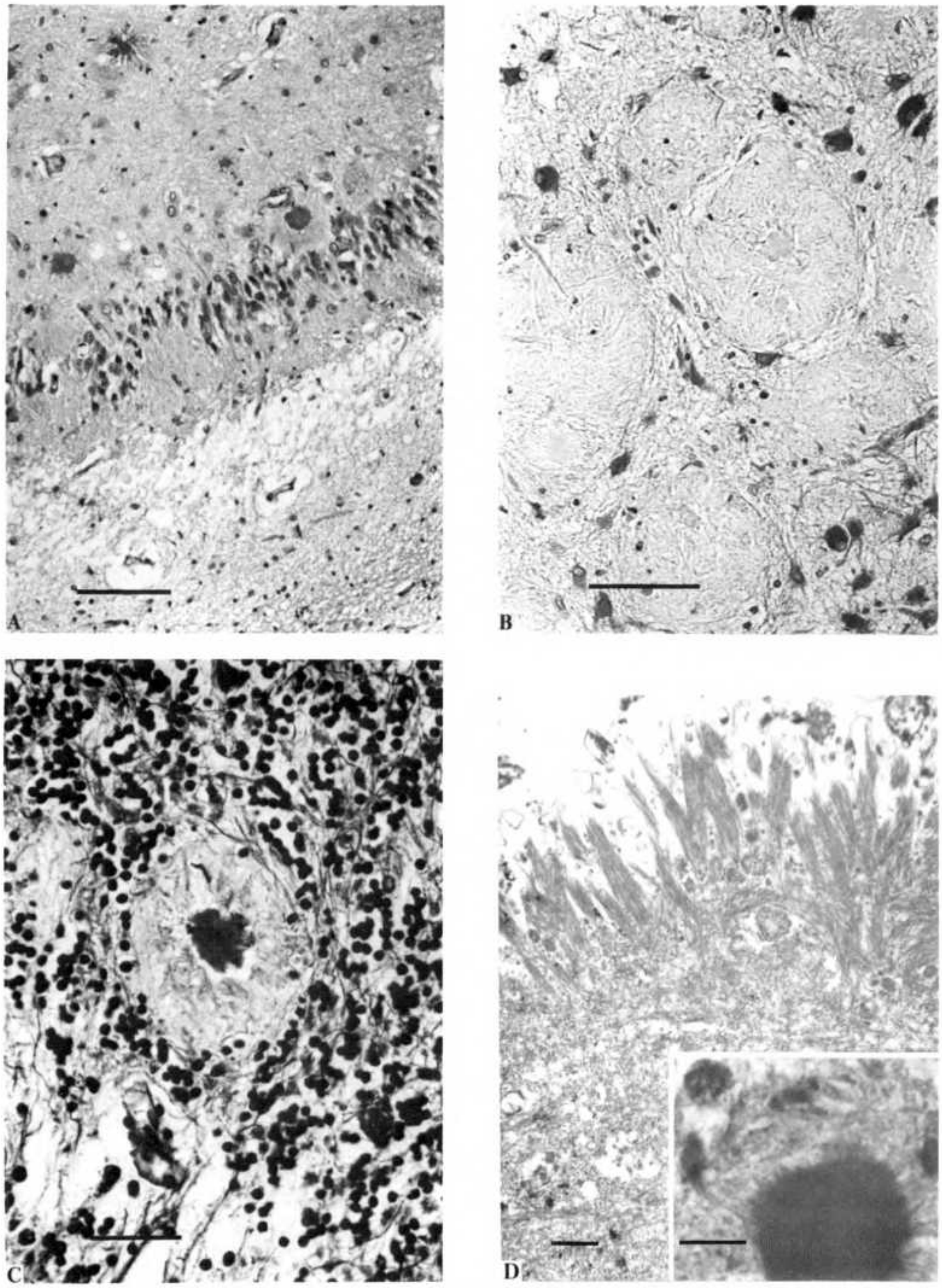

FIG. 6. A, 'large' plaques in the end-plate and fascia dentata of the hippocampus. PAS stain. Bar = 100 μm. B, 'large' plaques surrounded by numerous reactive astrocytes in the end-plate of the hippocampus. GFAP stain. Bar = 50 μm. C, 'large' plaque in the cerebellar granular cell layer. Bielschowsky silver stain. Bar = 50 μm. D, electron micrograph of a 'large' cortical amyloid plaque showing a core with fibrillary material and peripheral radiating processes. Bar = 0.5 μm. *Insert*: for comparison, the light microscopic picture of the core of a 'large' plaque from the inferior parietal lobule. PAS stain. Bar = 20 μm.

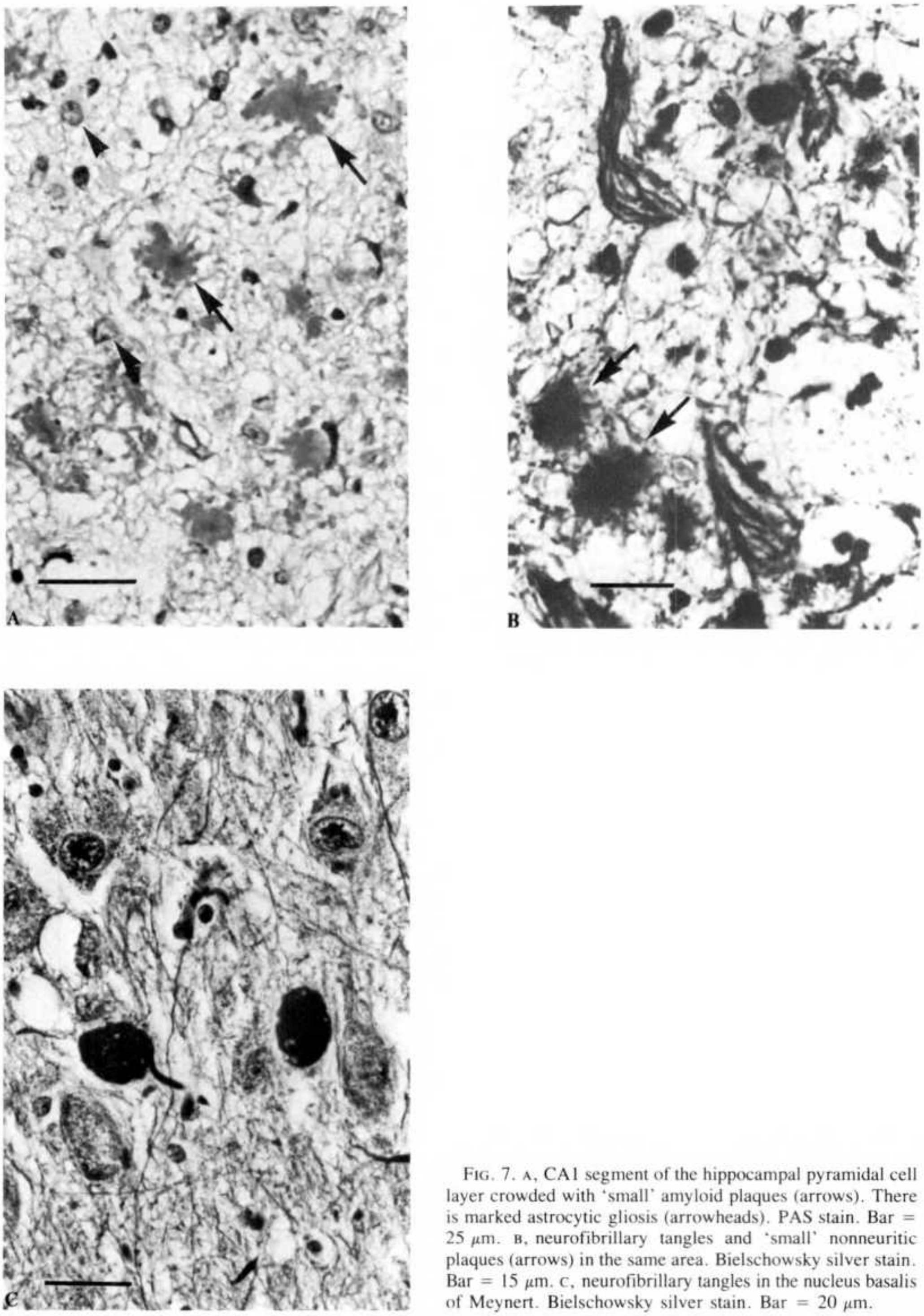

FIG. 7. A, CA1 segment of the hippocampal pyramidal cell layer crowded with 'small' amyloid plaques (arrows). There is marked astrocytic gliosis (arrowheads). PAS stain. Bar = 25 μm. B, neurofibrillary tangles and 'small' nonneuritic plaques (arrows) in the same area. Bielschowsky silver stain. Bar = 15 μm. C, neurofibrillary tangles in the nucleus basalis of Meynert. Bielschowsky silver stain. Bar = 20 μm.

uncommonly had a strongly congophilic core. When they had a dense core these plaques were very similar to the large plaques, except that they contained a centrally or more peripherally arranged capillary whose lumen was often completely or nearly completely obliterated. These plaques were seen in the molecular and granular cell layers of the cerebellar cortex and also in the cerebral cortex and white matter. Most of the plaques in the cerebral and cerebellar cortex and white matter seemed to be perivascular in origin.

With Bielschowsky preparations the cores of all three types of plaques were argyrophil, but only a minority of the large plaques in the hippocampus, amygdala and subiculum seemed to contain dystrophic neurites, resembling neuritic plaques of Alzheimer type.

The distribution and frequency of amyloid plaques in different neocortical areas and the hippocampal formation are shown in Table 4. The number of amyloid plaques/mm^2 is given. Statistical analysis revealed that cortical areas of the parieto-occipital region contained a significantly larger number of amyloid plaques than frontal cortex ($P < 0.007$; Mann-Whitney U test).

Neurofibrillary tangles (NFTs)

NFTs were numerous from CA1 to CA4 segments of the pyramidal cell layer of the hippocampus, in prosubiculum, subiculum, para- and presubiculum, entorhinal cortex,

TABLE 4. DISTRIBUTION OF AMYLOID PLAQUES IN DIFFERENT AREAS OF CEREBRAL CORTEX

	Number of plaques (per mm^2)	
Area investigated	*Cortical*	*Subcortical white matter*
Superior frontal gyrus	0.2	1.3
Middle frontal gyrus	0.2	0.6
Inferior frontal gyrus	0.1	0.2
Orbital gyri	0.1	0.7
Gyrus rectus	0.1	0.5
Cingulate gyrus	0.0	0.2
Motor cortex	0.4	0.2
Sensory cortex	0.3	0.1
Inferior parietal lobule	1.0	0.7
Paracentral lobule	0.4	0.2
Precuneus	0.1	0.4
Superior temporal gyrus	0.6	0.4
Middle temporal gyrus	0.1	0.5
Inferior temporal gyrus	0.4	0.9
Fusiform gyrus	0.3	0.5
Lingual gyrus	0.8	0.6
Hippocampal gyrus (entorhinal cortex)	0.3	0.7
CA1	63.0	0
CA2–3	27.3	0
CA4	34.1	0
Dentate fascia	12.5	0
Prosubiculum	45.1	0
Subiculum	2.3	0
Pre and parasubiculum	1.3	0
Striate cortex	3.0	0.6
Occipital gyri	2.8	0.4

lingual gyrus, and amygdala (fig. 7B). They were also found in the nucleus basalis of Meynert and pontine raphe nucleus (fig. 7C). Few neurons remained in the pyramidal cell layer of the hippocampus that did not show this change. From the prosubiculum to the lingual gyrus NFTs were mainly seen in the superficial areas of the cortex, where they were found in great number.

Other findings

Subpial gliosis was often seen over some of the gyri, particularly in the medial temporal cortex. The cerebral cortex was generally well populated with neurons and no gliosis was seen in the deeper cortical layers. There were, however, several small ischaemic lesions and also a few small mainly perivascular, haemorrhagic foci composed of haemosiderin-laden macrophages.

Myelin preparations showed significant rarefaction and pallor of the hemisphere white matter affecting all major regions. These changes were generally more pronounced in the corona radiata and periventricular areas, while the parietal and occipital white matter, specifically around the trigone and occipital horn of the lateral ventricle, appeared to be the most severely affected. The myelin loss was patchy and tended to spare the subcortical U fibres. It was always accompanied by axon damage and loss. In the affected areas astrocytic gliosis was constant but variable. There was several small lacune-like lesions in the frontal and more often in the parietal white matter. The penetrating small arteries and arterioles of the cerebral white matter were among those most severely involved by amyloid deposition. Several vessels with markedly thickened walls and very narrow lumina were present, especially in the frontal and parietal lobes (fig. 5A). Close to one of the lacunes in parietal white matter a small artery with severe amyloid deposition, 'double barrelling' and fibrous occlusion of its lumen was found.

The lentiform and caudate nuclei were normal. The blood vessels in these structures were only slightly involved. However, the small vessels of the thalamus were more significantly affected by amyloid deposition. In the ventrolateral nucleus there was a small cavity partly occupied by lipid-laden macrophages. The subthalamic nucleus was normal.

The changes in the cerebellum were widespread and severe, resulting in disruption of the structure in many areas. Congophilic angiopathy of the small arteries, arterioles and frequently capillaries, as well as the presence of amyloid plaques, most frequently perivascular, were all prominent features. Structures near to the midline, including the vermis, were among those most severely affected. There was some diffuse cell loss in the granular cell layer and more severe Purkinje cell loss. Axonal torpedoes were numerous. There was moderate to severe isomorphic gliosis in the molecular layer. In addition there were focal ischaemic lesions with tissue necrosis and cavitation in the cerebellar cortex and white matter. There was gliosis in and around the hilum of the dentate nucleus, which also showed neuron loss.

In the mesencephalon slight periaqueductal gliosis was present. In the rostral pons there was very slight astrocytic gliosis in the paramedian reticular formation.

Myelin pallor due to long tract degeneration was seen in the pyramids of the medulla. In addition, other white matter structures, notably the middle segment of the restiform body, and the ventral spinocerebellar tract, were also involved. There was severe diffuse neuron loss accompanied by gliosis in both inferior olives. There was significant pallor of myelin staining and also loss of axons of the efferent fibres in the hilum and also that of the circumamicular fibres. In the dorsal part of the medial accessory olive there was neuronal loss and gliosis.

Only the lower cervical and thoracic portions of the spinal cord were available for neuropathological examination. Mild pallor of myelin staining of the gracile and cuneate fasciculi and also of the lateral funiculus involving the corticospinal and dorsal and ventral spinocerebellar tracts was found. The uncrossed corticospinal tract was also involved. In addition, the involvement of the subpial region in the whole circumference of the cord was a general feature. A few large plaques and perivascular plaques were seen in both grey and white matter.

Electron microscope findings

The walls of arterioles and affected capillaries were completely replaced by interwoven bundles of ~10 nm filaments which were rather short and were arranged in a disorderly way. These filaments tended to radiate into the surrounding neural tissue (fig. 5B). No basement membrane was found around the affected vessels. The amyloid deposits in plaques showed crisscrossing and, at the periphery, radially arranged fibrils with an approximate diameter of 10 nm (fig. 6D).

DISCUSSION

Clinicopathological correlation

The clinical features of the condition may be summarized as a dominantly inherited disorder, with onset around the fifth decade, characterized by progressive dementia, spasticity and cerebellar ataxia. These three elements differ in degree between cases. Stroke-like episodes occur occasionally. The pathological features are consistent in the 6 cases autopsied to date and the following features have been common to all; severe and widespread amyloid angiopathy of the brain and spinal cord with perivascular amyloid plaque formation; periventricular white matter change resembling Binswanger's leukoencephalopathy; small haemorrhagic lesions and infarcts; nonneuritic amyloid plaques affecting cerebellum, hippocampus, amygdala and occasionally cerebral cortex; and neurofibrillary tangle formation in hippocampal neurons. Inconstant features have been: senile (neuritic) plaques in the hippocampus in IV13 (Worster-Drought *et al.*, 1940, Case 1) and V4 (Griffiths *et al.*, 1982, Case 1). Amyloid plaques were more widespread in some cases, being found in white matter, cerebral cortex and brainstem (V4, V7 and V41). In 1 case (V7) the vessels of the spinal cord were relatively spared. It is interesting to note that haemorrhagic changes were most prominent in case V4 who was known in life to have had hypertension and whose clinical course was punctuated by at least one stroke which may have been due to a cerebellar haemorrhage.

We agree with Worster-Drought *et al.* (1940, 1944) that the subcortical ischaemic change is likely to have been a direct result of the amyloid angiopathy, and to have contributed substantially to the clinical course of the disease. As in Binswanger's leukoencephalopathy, chronic hypoperfusion of subcortical white matter secondary to involvement of penetrating arterioles is the likely mechanism (De Reuck, 1980). In recent years the occurrence of cerebral amyloid angiopathy in a variety of conditions has become better appreciated (*see* Vinters, 1987, for a recent review) and Binswanger's subcortical leukoencephalopathy has been reported in association with sporadic cerebral amyloid angiopathy in a group of elderly patients (aged from 52 to 83 yrs) with and without hypertension (Gray *et al.*, 1985). We suggest, however, that the early appearance of spasticity and its ultimate severity is difficult to account for entirely on the basis of the white matter ischaemic change. Perhaps the involvement of the spinal cord vessels followed by ischaemic damage to the cord parenchyma may, at least in part, be responsible for this. The plaque formation and neuronal degeneration in hippocampus and cerebellum and also ischaemic changes in this latter structure would account for the prominent and early amnestic syndrome and ataxia, respectively (Zola-Morgan *et al.*, 1986; Ball, 1988).

Relationship to other familial conditions

We cannot attempt to provide a definitive classification of this disorder but wish to compare it with a number of other familial conditions. Whether this disorder is unique or a variant of another disease discussed below will not be known until the identity of the amyloid protein has been determined and/or the defective genes have been analysed in detail.

Familial Alzheimer's disease

Since 1932 at least (Schottky, 1932), there have been a number of reports of familial Alzheimer's disease. A recent report describing 24 kindreds with pathologically verified familial Alzheimer's disease (Bird *et al.*, 1989) has emphasized the phenotypic heterogeneity of the disorder which can be associated clinically with spasticity and ataxia. Pathologically, neurofibrillary tangle formation in hippocampal neurons is, of course, characteristic: congophilic angiopathy can occur, occasionally with ischaemic changes similar to those seen in this family (Corsellis and Brierley, 1954; Mandybur, 1975; CDH family of Bird *et al.*, 1989): amyloid plaques may be seen in the cerebellum (Pro *et al.*, 1980). However, we agree with both Worster-Drought *et al.* (1940) and Griffiths *et al.* (1982) that as far as the neuropathological evidence is concerned, the important distinction between these cases and Alzheimer's disease is the plaque morphology and, to some extent, the white matter destruction. Some recent workers have suggested that plaque morphology may not be as reliable a means of classifying plaques as immunohistochemistry (Kitamoto *et al.*, 1988; Roberts *et al.*, 1988). Indeed, positive immunostaining with antiprion protein (PrP) has resulted in a family previously reported as familial Alzheimer's disease being reclassified as a variant of GSS (Heston *et al.*, 1966; Nochlin *et al.*, 1989; *see* below). However, the present authors are unaware of any example of nonneuritic amyloid hippocampal and cerebral cortical plaques of the type seen in this family that have been shown to stain with anti-β-peptide which is (in Alzheimer's disease) known to be the constituent protein of cerebrovascular amyloid (Glenner and Wong, 1984), of cortical neuritic plaques (Masters *et al.*, 1985), and also of the rare diffuse and compact cerebellar amyloid plaques in Alzheimer's disease (Yamaguchi *et al.*, 1989).

Familial cerebral haemorrhage with amyloidosis

Autosomal dominant hereditary cerebral haemorrhage occurring in Icelandic families was first described by Arnason (1935). Gudmundsson *et al.* (1972) demonstrated that cerebral amyloid angiopathy was responsible and it has subsequently been shown that the amyloid protein is a variant of cystatin C or γ-trace (Cohen *et al.*, 1983; Jensson *et al.*, 1987). Clinically, the course of the illness depends on the severity of the cerebral haemorrhages: an affected individual may be struck down by a catastrophic stroke or may live for many years sustaining multiple strokes of varying severity. The onset of symptoms is early (mean age around 30 yrs). A chronic progressive history, such as is most typical in the present family, is unusual. In the Icelandic cases the distribution of the amyloid angiopathy is very extensive and it is found in cerebral, cerebellar and brainstem arteries, but there is no plaque formation and neurofibrillary tangles have not been reported.

Hereditary cerebral haemorrhage with amyloidosis in Dutch patients is another autosomal dominant disease in which, characteristically, healthy normotensive individuals spontaneously develop intracerebral haemorrhage although at a later age than in the Icelandic type (mean around 55 yrs) (Wattendorff *et al.*, 1982; Luyendijk *et al.*, 1986). Pathologically, the distribution of the amyloid angiopathy is in the main limited to the cerebral cortex and leptomeninges, plaques resembling senile plaques are found in the cortex, there are no neurofibrillary tangles and the amyloid protein has been identified as being β-peptide (Van Duinen *et al.*, 1987).

Important differences exist between these disorders and that reported here, both clinically and pathologically.

Gerstmann-Sträussler-Scheinker disease (GSS)

It has been established that examples of this familial disease (first described by Gerstmann *et al.*, 1936) and conditions that have been classified as familial examples of Creutzfeldt-Jakob disease (CJD) or spongiform encephalopathy (e.g., Adam *et al.*, 1982) are related to the transmissible encephalopathies, namely sporadic CJD and kuru in man and scrapie in sheep and other mammals. This relationship was first suggested by pathological similarities (Seitelberger, 1962) and subsequently by transmissibility (Tateishi *et al.*, 1979; Masters *et al.*, 1981*b*). PrP antibody immunoreactivity of GSS plaques has been demonstrated (Roberts *et al.*, 1986; Baron *et al.*, 1988; Kitamoto *et al.*, 1988). Very recently mutations of the PrP gene on chromosome 20 have been linked to the disease in some families (Collinge *et al.*, 1989; Hsiao *et al.*, 1989; Owen *et al.*, 1989). Most nonneuritic cerebral cortical plaques that have been examined with immunostains have been shown to be PrP positive, but this may not be universally true (Rosenberg *et al.*, 1989) and plaque morphology alone may not be a reliable guide to the constituent amyloid protein.

The clinical features and pathological findings are variable, even within different members of the same family. In typical GSS there is a chronic progressive history of predominantly cerebellar symptoms with dementia. Spasticity and lower limb areflexia are common but not invariable features. Where the clinical history is long and is 'characteristic' of GSS rather than CJD, atypical amyloid plaques of the type observed in the present family are always found in cerebellum and cortex. The only significant difference between the plaque morphology in the present family and GSS is that the plaques are frequently multicentric in GSS (Boellaard and Schlote, 1980; Schlote *et al.*, 1980). Although neurofibrillary degeneration has only rarely been described in GSS (*see* de Courten-Myers and Mandybur, 1987), it appears that in a subgroup of patients the presence of NFT-s is a constant finding (Hsiao *et al.*, 1989). Rare NFTs were noted in a recently described familial dementia with anti-PrP positive plaques (Nochlin *et al.*, 1989).

However, amyloid angiopathy is not common in GSS. There is, to the authors' knowledge, only 1 example of a case of proven familial GSS in which cerebral amyloid angiopathy was a prominent feature (Case 3 of Adam *et al.*, 1982), although there are other cases which may be examples of GSS (not established on the basis of either immunostaining or transmissibility) with amyloid angiopathy (Kornfeld, 1984; de Courten-Myers and Mandybur, 1987; Koo *et al.*, 1987). Amyloid angiopathy also occurs in animal scrapie (Bendheim *et al.*, 1984; Gilmour *et al.*, 1986). Furthermore, in those cases of GSS or possible GSS in which amyloid angiopathy has been found, immunostaining to confirm that the vascular amyloid protein is also PrP has not been carried out. The importance of this has recently been highlighted in a case of sporadic CJD with amyloid angiopathy (Keohane *et al.*, 1985) in which it has been found that the amyloid angiopathy stained with anti-β-protein, while the cerebellar plaques show anti-PrP immunoreactivity (Roberts *et al.*, 1988).

Familial oculoleptomeningeal amyloidosis

Oculoleptomeningeal forms of familial amyloidosis occur (*see*, e.g., Goren *et al.*, 1980); recently an unusual variety has been described in which meningeal involvement resulted in cerebral haemorrhage and myelopathy (Uitti *et al.*, 1988). An anomalous prealbumin (transthyretin) was identified in serum. There is, however, no example known to the authors of prealbumin being implicated in cerebral amyloid angiopathy or parenchymal cerebral amyloid deposits.

Familial multi-infarct dementia

There have been a few reports of familial disorders characterized by dementia and other evidence of CNS vascular damage, some with an autosomal dominant mode of transmission (Sourander and Wålinder, 1977; Stevens *et al.*, 1977; Yokoi and Nakayama, 1985; Sonninen and Savontaus, 1987). Pathological data are available in 2 families in which minor stroke-like episodes occurred and dementia developed at an early age. Small vessel arteriopathy, fibrinoid necrosis, inflammatory infiltrate, lamellar elastosis, hyaline degeneration of the vessel wall and occlusion of the lumen were observed, but there was no deposition of amyloid (Sourander and Wålinder, 1977; Stevens *et al.*, 1977). In the Japanese cases (Yokoi and Nakayama, 1985) the symptoms also started at a young age (25–29 yrs), but the presentation was slowly progressive rather than stepwise, with the development of memory disturbance, dementia and spastic paraplegia. In all these cases a tendency to baldness and 'lumbago' were described. Pathologically, extensive white matter damage, seen as pallor and rarefaction on myelin preparations, as well as cystic infarcts in the white matter and basal ganglia, were detected. The small arteries of the brain parenchyma and leptomeninges presented severe arteriosclerosis and only the pial arteries of medium size showed occasional staining for amyloid.

Conclusions

There are a number of familial disorders in the literature where cerebral amyloid angiopathy and plaque formation have been the major pathological findings. Many of these were discussed by Griffiths *et al.* (1982) and presented by them in tabular form (the cases of van Bogaert *et al.*, 1940; Lüers, 1947; Corsellis and Brierley, 1954; Neumann, 1960; Hollander and Strich, 1970; Gerhard *et al.*, 1972). To the list should be added the family described more recently by Love and Duchen (1982). This case showed autopsy features similar to those reported here except that the hippocampal involvement was less severe. In life the proband and 3 affected relatives had had cerebellar ataxia without dementia. The published details of the family make it unlikely that the case was descended from any as yet untraced descendants of III2, III5 or III6 in fig. 1.

It is unlikely that an attempt to classify these disorders based on either clinical features or neuropathological features such as plaque morphology will be successful. It is the identification of the amyloid protein and the defective genes that is critical, and in the family reported here is the subject of further investigation.

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APPENDIX

Case histories

The sources of the information given below are the papers of Worster-Drought *et al.* (1933, 1940, 1944) and Griffiths *et al.* (1982); genealogy compiled in 1933 by the husband of IV15 for Worster-Drought; the accounts given by IV15 and her husband to the house officer when IV12 was admitted to the National Hospital for Nervous Diseases (NHND) in 1924 and 1926; the NHND case notes of IV12, IV13, V38, V36; Dr S. A. Hashimoto of Vancouver, BC, who examined V45 in 1973–1974 and Dr R. Grosch of New Westminster, BC, who examined her in 1988; Dr P. O. Williamson of St Leonards, NSW, who examined V2 in 1987; the notes of the late Dr R. A. Griffiths; and information from several surviving family members.

I1, I2. No information.

II1, female. Born 1830, died 1883. Taken ill at age 40 yrs, died age 53. Said to have had a stroke and died of paralysis.

II2, female. Reputed to have had a similar history to II1 but nothing else known of her.

II3. There is said to have been a brother and a sister but nothing is known of them.

III1, female. Born 1851, died 1903. Although it is not stated in Worster-Drought *et al.* (1940, 1944), it is recorded in the NHND case notes for IV13 that she died of paralysis; the informant was IV15. In Griffiths *et al.* (1982) she is case 'A' in the published pedigree, said to have died from 'creeping paralysis' and to have been confined to a wheelchair towards the end of her life. At some stage in the illness she was treated with electroconvulsive therapy for depression.

III2, male. Born 1853, died 1913. Developed paralysis at age 57 yrs and died at 60. Two children were unaffected in 1933. No further information.

III3, female. Born 1855, died in 1909 aged 54 yrs in Tooting Bec Asylum. Illness began at 44 with paralysis followed by dementia. Was examined when 50 in 1905 by Dr Farquar-Buzzard. Six months previously lost power in left hand which recovered in one month. Her memory had been impaired for 6 months and there had been frequent giddiness and some difficulty in swallowing. Three weeks previously she had lost her speech. On examination she was noted to have defective memory and weakness and ataxia of limbs. She was also dysarthric and lethargic. According to an account given by IV8 she became very slack with the household, wanting to sit still for hours, taking no interest in anything and if asked to do anything would fly into a temper. In the course of the illness she went to the door to see the milkman and when she got there she was unable to speak properly. She burst out crying and said that she had her mother's illness. After this she spoke in a spluttering kind of way and shuffled her feet when walking.

III4, female. Born 1857. Entered Banstead Asylum aged 48 yrs and died there at age 53. Developed dementia first, then paralysis.

III5, female. Born 1861. Died aged 66 yrs. Taken ill with paralysis at 48. Dementia less severe. Bedridden for 16 yrs; towards the end limbs and tongue useless but could understand everything said to her. Did not require certification. Had 5 sons and 1 daughter whose ages would have ranged from 85 to 104 if alive in 1989 but nothing is known of them except that none was affected in 1933.

III6, female. Born 1865. Died 1915 at 50 yrs having developed paralysis only 2 yrs previously. She had 9 children; none was affected in 1933; ages would have ranged from 81 to 101 if alive in 1989.

III7, male. Born 1870, died later than 1933. Neither he nor his 2 children were affected in 1933 but no more is known of them.

III8, female. Born 1872. Mentally subnormal. Unable to walk until 5 yrs and died aged 14 from scarlet fever.

III9, female. Born 1874. Well at age 60 yrs in 1933.

III10, female. Born 1875. Described as fit when 58 yrs of age. Had 12 children. The eldest known to be alive in 1933 would be 84 and the youngest 71 in 1989.

IV1, male. Born approximately in 1896. Died aged 53 yrs. Married with no descendants. His wife had been a neighbour of IV1 and knew of the family illness. He had a stepdaughter who remembers that he developed an unsteady gait in his 5th decade. He was a sailor and was badly burned while at work. A doctor advised that he should stop work. Loss of memory occurred relatively late and he died in Chartham Asylum near Dover. No stroke-like episodes.

IV2, female. Born 1897, died aged 52 yrs. Cause of death on the death certificate given as 'familial muscular dystrophy'. At age 43 she developed headaches and other symptoms including diplopia which led to a posterior fossa craniotomy carried out at the NHND for a suspected tumour. Thereafter she developed progressive dementia and paralysis and died in St Luke's Hospital, Chelsea, having become totally dependent. (B4 in Griffiths *et al.*, 1982.)

IV3, female. Born 1882. Died aged 56 yrs in St Bartholomew's Hospital, Rochester, Kent. Became ill at age 46 when she began to walk 'crooked' and also complained of headaches. In 1931 her daughter married and she attended the wedding being unable to walk or feed herself and incontinent of urine although still able to comprehend the significance of the event. (B5 in Griffiths *et al.*, 1982.)

IV4, female. Born 1889, died aged 74 yrs. Cause of death was a cerebral haemorrhage but there was no progressive disease. One son died in 1942 (drowning). Survived by a son of 76 and a daughter of 62 both of whom are well in 1989.

IV5, male. Date of birth uncertain. Died aged 80 yrs. Cause of death unknown but there was no progressive illness. Married but had no children.

IV6, male. Born 1890. Lost a leg in an accident on the railway at age 18 yrs. Died aged 51. Became ill in his mid-40s with headache, deteriorating speech and memory. The family recall a personality change—became 'bad-tempered'. Three daughters who are alive and well in 1989. Had 1 son who died of the disease.

IV7, female. Born 1880, died aged 63 yrs. Cause of death given as cerebral thrombosis; no progressive illness leading up to this. Her 7 children are all deceased but none is known to have had the disease.

IV8, male. Date of birth uncertain, died aged >70 yrs. Cause of death unknown but in the family he is considered not to have had the disease.

IV9, female. Born 1879, died aged 56 yrs. Illness began with 'collapse' at age of 50, progressive thereafter and died in Buckland Hospital, Dover; no records survive.

IV10–11. Nothing is known of the 2 children of III2 except that both were unaffected in 1933 when their ages would have been greater than 50.

IV12, female. Born 1879, died 1933 aged 54 yrs. Developed paralysis at 44 and progressive dementia ensued. Admitted to NHND at age 45; 4 months before this tried to get out of bed one day and found that she could not stand or talk properly. On examination she had dysarthria, was emotional and complained of giddiness. Her memory was poor and she spoke in a slow halting fashion. Cranial nerves were normal and there was limb weakness and ataxia but normal reflexes. CSF examination was normal. Two yrs later she was readmitted. She complained of occasional dizziness when out in the street and had fallen several times. Dysarthria was about the same but memory worse. Thereafter her speech and memory deteriorated and she developed spasticity. Her gait was noted to be spastic 3 yrs before her death. Bedridden and incontinent during remainder of her life.

IV13, male. Born 1882, died 1936. At 46 yrs developed a personality change become ill-tempered. At 47 noticed difficulty walking after drinking 1 glass of beer and the following day reported for duty at the wrong time (he was an engine driver). When first examined at 47 his gait was normal but there was increased tone in lower limbs and increased reflexes. Forgetfulness, irritability and difficulty walking progressed. At 50 he was discharged from his work following a medical examination. By 51 he had become apathetic and incontinent, had a spastic gait and was dysarthric with a poor memory. He became severely amnesic, tone was increased in all 4 limbs and his gait was spastic. He was admitted to the NHND in 1934 at the age of 52 under Dr MacDonald Critchley. There was a global dementia and mild nystagmus. He was very spastic with exaggerated reflexes but flexor plantar responses. The CSF protein was 1.1 g/l. In the last year of his life he was unable to walk or feed himself and was doubly incontinent. He died aged 54. Autopsy findings were reported by Worster-Drought *et al.* (1940).

IV14, male. According to the account given by IV8 in 1934 this brother died at 38, unaffected by the illness although the cause of death is not known. No more is known of him and he does not appear in the previously published pedigree (Worster-Drought *et al.*, 1940, 1944).

IV15, female. Born 1889, died 1944 aged 56 yrs. At the age of 44 developed memory impairment and personality change, becoming irritable. Within a year she was unsure of her feet when walking. She was examined at age 51. Speech was slow and slurred, gait ataxic and there was slight horizontal nystagmus. All 4 limbs were spastic with ankle clonus but uncertain plantar responses. CSF examination was normal and (AEG) air encephalography showed dilatation of the lateral ventricles. Dementia progressed and she developed a severe spastic paraplegia and pronounced nystagmus. She died 'practically inanimate' at the age of 56. Autopsy findings were reported by Worster-Drought *et al.* (1944).

IV16, male. Born 1892. Died 1965 aged 73 yrs following influenza.

IV17, female. Born 1895, date of death uncertain. From the age of 43 yrs developed progressive memory impairment and difficulty in walking; became depressed and tearful. When examined at age 45 noted to have dysarthria, exaggerated tendon reflexes, spasticity and poor coordination of lower limbs. Details of the progression of the illness not known.

IV18, male. Born 1896. Died 1959 aged 63 of a myocardial infarction.

IV19–33. No information.

IV34–35. Well in 1933. No further information.

IV36–44. No information.

IV45–50. Six children of III10 died in infancy.

V1, 3, 6, 8, 9, 11, 13, 14, 23–26, 30, 37, 38, 42, 43, 44, 46. Alive and well in 1989.

V2, female. Born 1925, died aged 63 yrs. Was well until age of 57 when she had 4 episodes of tingling affecting right side of the body lasting 10 min on each occasion. For 1 yr had been unsteady on her feet. Long history of headache ascribed to migraine. Noted to have unreactive pupils, absent tendon reflexes and mild gait ataxia. CT brain scan within normal limits. Two yrs later, balance had deteriorated further, she had occasional myoclonic jerks and some memory impairment. Psychometric assessment revealed 'reasonable' verbal and performance IQ but impaired memory. By age of 60 had developed dysarthria and diplopia with further deterioration in gait and memory. Plantar responses then extensor. Became depressed and died at home 3 yrs later. She was in the bath attended by her husband, began to complain of severe chest pains and died 30 min later from a presumed myocardial infarction. When she was 60, 3 yrs following the onset of the illness, an MRI scan showed extensive white matter high signal with 'U' fibre sparing (*see* fig. 3). Shortly before death a further CT scan performed because of persistent headaches showed low attenuation in frontal and occipital periventricular regions. (C4 in Griffiths *et al.*, 1982.)

V4, female. Born 1905, died aged 61 yrs. Married with no children. At age of 54 developed ataxia and dysarthria; 1 yr later was found to have a spastic-ataxic gait and nystagmus. She was hypertensive. CSF examination was normal. At age 56 her legs 'gave way' in the street and she became unconscious for 24 h. Three days later she was disorientated and dysarthric; had nystagmus and an extensor left plantar response. She never left hospital, lapsing into a vegetative state. A year before her death she was bedridden, unresponsive and doubly incontinent, lying in a flexed posture, with widespread muscle wasting, with spasticity, exaggerated tendon reflexes and extensor plantar responses. Her autopsy findings were reported by Griffiths *et al.* (1982; Case C6).

V5, female. Born 1906, died aged 80 yrs of an unrelated condition.

V7, male. Born 1915, died aged 56 years. At age of 50 he developed weakness of all 4 limbs, ataxia, dysarthria and memory impairment. He complained of pins and needles in the fingers of both hands. On examination he had a kyphoscoliosis which had been present from his teens, gait ataxia, dysarthria, and limb weakness and ataxia. Muscle tone and tendon reflexes were normal. AEG revealed moderate ventricular dilatation. CSF examination was normal. The disorder was progressive thereafter. He had a transient right abducens paresis. By age 54 dementia was obvious and the disorder progressed to a vegetative state with marked spasticity. An autopsy study was reported by Griffiths *et al.* (1982; Case C9).

V10, male. Born ?1922. Died in the Second World War (drowning). No descendants.

V12, female. Born 1911. Alive and well in 1988 when she suffered a skull fracture and cerebral injury in a road traffic accident. Although she survived this she remains in hospital in 1989.

V15, male. Born 1915, died aged 51 yrs. At around age of 45 began walking as if drunk and complained of giddiness. Investigated at the Brook Hospital in 1964/1965. No records have survived. Progressive dementia and paralysis until his death. He married twice. One daughter died at age of 36 of cancer; his son from his second marriage survives him.

V16, female. Born 1901, died aged 80 yrs, 'cerebrovascular accident'. No progressive illness.

V17, male. Born 1903. Died aged 54 yrs, cancer.

V18, female. Born 1905. Died aged 78 yrs, 'cerebrovascular accident'. No progressive illness.

V19, female. Born 1909. Died aged 50 yrs, 'cerebral thrombosis'. No progressive illness.

V20, male. Born 1911, died aged 72 yrs. Two minor strokes in his late 60s. Died suddenly either from 'heart attack' or aortic dissection. Autopsy at Orpington Hospital.

V21, male. Born 1915. Died aged 73 yrs, haematemesis. Had had hypertension and renal failure.

V22, female. Born 1918. Died aged 68 yrs, myocardial infarction.

V27, female. Born 1899, died aged 4 yrs.

V28, female. Born 1901, died aged 55 yrs. In her fifth decade she became 'bad-tempered'. At age 50 she collapsed on a bus and the next morning was found to have weakness of left arm and leg. From that day she gradually deteriorated over 4 yrs by which time she could walk but swayed as if drunk. In the last 2 yrs of her life memory loss was profound.

Spent last 18 months in Leamington Park Hospital, became paralysed and developed contractures. Cause of death given on death certificate as 'multiple cerebral thromboses'. No autopsy. Case notes destroyed.

V29, male. Born 1902. Died 1979 aged 77 yrs, unaffected by the disease, carcinoma of prostate.

V30, female. Born 1903, alive and well in 1989.

V31, male. Born 1904. Died aged 72 yrs, unaffected. 'Cancer of liver' on death certificate.

V32, male. Born 1906. First symptoms around age 40 yrs. Died 1958 aged 52 in St Augustine's Hospital, Canterbury, of the disease. No further details. No autopsy.

V33, male. Born 1910, died 1965 aged 54 yrs. At age 48 developed paralysis but precise details are not known. Four children, including twins. In last 2 yrs of his life was paralysed and in the last year mute. He died in Hellingley Hospital, Hailsham, Sussex. It is understood that an autopsy was carried out.

V34, male. Born 1913. Died aged 74 yrs in Ontario, Canada. Four children. Unaffected by the disease.

V35, male. Born 1922, died 1955 aged 33 yrs. At age 25 (when his wife first met him) he was unwell, being very forgetful and would from time to time wake with severe headache and vomiting. He was training to be a telephone engineer when, at the age of 31, he was found to have hypertension and was investigated at King's College Hospital, London. A diagnosis of essential hypertension was made. He continued to have difficulties with memory but otherwise did not develop any specific symptoms until his sudden death of a ruptured aorta. It is likely that a coroner's postmortem was carried out. It remains uncertain whether or not he was affected by the disease.

V36, female. Born 1909. At age of 24 yrs described as myopic and very nervous. No further details.

V38, male. Born 1919. Retired for social reasons at 63 yrs. When examined at age of 68 was entirely well; remains so in 1989.

V39, female. Born 1920. Was seen at NHND at the age of 61 yrs when there was no evidence of intellectual deterioration on formal psychometric testing; a CT scan was normal.

V40, male. Born 1923. Died 1972 aged 48 yrs of a cerebral haemorrhage. Died suddenly at home and a coroner's autopsy was carried out at Pontypool, Wales. He had asthma as a child but was otherwise well until this episode; had become a skilled glassblower. The cause of death was a ruptured berry aneurysm of the circle of Willis; the brain was not examined histologically.

V41, female. Born 1923, died aged 65 yrs. Well until 56 when she noticed difficulty in walking, clumsiness of her hands and slurring of her speech. At about the same time noticed impairment of her memory and took to writing things down, otherwise would go shopping repeatedly for the same items. Mild urgency of micturition but no other specific symptoms. Was investigated at NHND in 1981, a year after onset of symptoms.

Psychometric assessment showed a verbal IQ of 115 and a performance IQ of 104 on the WAIS with a predicted IQ of 116 on a reading test. Memory functions were weak, scoring below average on a forced choice recognition test and there was patchiness in her performance on perceptual tests. Her speech was mildly dysarthric. Spastic ataxic gait. First degree nystagmus observed on right and left gaze and positional nystagmus of central type with head back to left and right; optokinetic nystagmus grossly deranged horizontally and absent vertically. Caloric testing revealed exaggerated symmetric responses with no enhancement in the dark. Cranial nerves were otherwise normal. Spasticity in all 4 limbs without weakness. Jaw jerk and all tendon reflexes exaggerated, abdominal reflexes absent and plantar responses bilaterally extensor. Mild finger-nose and heel-shin ataxia but no sensory deficit. CT scan (fig. 2) showed mild cerebral atrophy and extensive bifrontal and biparietal white matter low attentuation. Nerve conduction studies, EEG, SEPs, BAEPs and VEPs within normal limits. CSF examination normal with no oligoclonal IgG bands on electrophoresis.

At age of 64 was totally dependent, being cared for in a nursing home, unable to swallow liquids and choking on solids. When visited by her husband she would say his name but nothing else. In the last year of her life she was observed to turn to a sound but nothing more; was very spastic. An autopsy was performed and is reported in this article. She had no descendants.

V45, female. Born 1924, died aged 64 yrs. Became ill in 1966 with impaired memory and deterioration in reading and writing. Had 2 episodes of loss of consciousness in 1970 and 1973. In 1973 she was being treated for hypertension and was seen by a neurologist who found her to be severely demented with good power in the limbs but spasticity and a left extensor plantar response. An AEG showed severe atrophy but a left carotid angiogram was normal. An EEG showed a focal abnormality in the mid portion of the right hemisphere and a lesser abnormality on the left. By the following year she had deteriorated. Her speech was unintelligible and her legs had become extremely spastic. She had a left hemianopia and both plantar responses were extensor. At about this time a diagnosis of Alzheimer's disease was made. At age of 63 she was examined and found to be requiring total nursing care, was doubly incontinent and unable to feed herself. For 2 yrs had shown no sign of recognizing her family but was still able to follow with her eyes. On examination she was lying mute with no indication that she understood what was said to her. She followed a moving object and nystagmus was noted. Primitive reflexes were present. There were flexion contractures of upper and extension contractures of lower limbs. Tendon reflexes were diminished with bilaterally extensor plantar responses. She died a few weeks following this assessment.

The following members of generation VI were alive and well in 1989 (*see* fig. 1 for ages, where known): 1–20, 23–28, 30–54, 56–58.

VI21, female, Date of birth uncertain. Died aged 36 yrs of cancer. Has 2 sons and 2 daughters who live in the USA.

VI22, male. Date of birth uncertain. Died aged 29 yrs, supposedly of a 'heart attack' but details not known.

VI32, female. Born 1940. Died aged 46, carcinoma of bronchus.

VI55, female. Born 1963. At age 13 yrs saw a neurologist. For several months she had been liable to trip. Noted to have weakness bilaterally of ankle dorsiflexion and eversion. She was obese and of poor intellectual development. No other abnormal physical signs. Three years later she was noted again to have a kyphosis and mild pes cavus. At age of 25 she was evaluated by Professor P. McGeer. It is considered possible, but not certain, that she is affected. Figure legends

Brain (1990) **113**, 749–766

TROUBLED LETTERS BUT NOT NUMBERS

DOMAIN SPECIFIC COGNITIVE IMPAIRMENTS FOLLOWING FOCAL DAMAGE IN FRONTAL CORTEX

by STEVEN W. ANDERSON, ANTONIO R. DAMASIO *and* HANNA DAMASIO

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SUMMARY

A well educated right-handed woman developed severe and stable alexia and agraphia following a circumscribed surgical lesion in the left premotor cortex. The lesion was located in Brodmann's field 6, above Broca's area, in the region traditionally referred to as Exner's area. The alexia and agraphia occurred in a pure form, that is, in the setting of otherwise normal cognitive and neurological function. She was not aphasic or hemiparetic and her visual perception, intellect, memory, oral spelling and drawing were normal. The patterns of impairment of reading and writing closely paralleled one another. Reading of single words and letters was severely impaired, and she was entirely unable to read sentences. She was virtually unable to write recognizable letters, could write no words, and her writing attempts were severely distorted spatially. By contrast, she could easily read all numbers and nonverbal symbols, and she was equally able to write numbers and perform written calculations without difficulty. These striking dissociations provide further evidence of the domain specificity of cognitive/neural representations. They also point to the possible role of premotor cortices in the coactivation of precise sequences of motor and sensory activity patterns involved in reading and writing.

INTRODUCTION

The case described here afforded the opportunity of studying alexia with agraphia together in a pure form, that is, uncontaminated by aphasia, apraxia, or hemiparesis. Unlike pure alexia (alexia without agraphia or aphasia), which is not uncommon and has permitted the study of some of its component cognitive defects as well as the delineation of its anatomical correlates (Déjerine, 1892; Geschwind, 1965; Greenblatt, 1973; Friedman, 1982; Damasio and Damasio, 1983), the isolated appearance of alexia with agraphia is exceedingly rare. When they are caused by temporoparietal lesions, the two defects are almost invariably accompanied by fluent aphasia. In cases associated with frontal lesions, they invariably occur in the context of nonfluent aphasia and often right hemiparesis (Benson, 1977).

In the present case, alexia and agraphia were associated with an unusually circumscribed lesion within the left frontal lobe. In general, the left frontal cortices have not been

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associated with alexia except in the setting of aphasia, and have only been associated with agraphia in a small number of old case reports. Because of the language and motor impairments usually associated with left frontal lobe damage, the teasing out of component defects and the investigation of neural substrates of frontal alexia and agraphia have been manifestly difficult. To our knowledge, pure alexia caused by a focal frontal lobe lesion has not been reported. Furthermore, despite widespread acceptance of the notion that pure agraphia may result from damage to an area of the left superior premotor cortex known as Exner's area, there has been little study of such a defect (Kaplan and Goodglass, 1981; Roeltgen, 1985).

Of no lesser interest was the finding that in spite of severely impaired word and letter reading and writing, the patient revealed entirely normal reading and writing of figures and numbers, as well as normal calculation. This neuropsychological profile, together with the finding of a circumscribed area of damage in the left premotor cortex, provides further evidence for the separation of neural systems underlying recognition and performance in terms of knowledge domain. It also raises hypotheses regarding the cognitive and neural networks that can possibly subserve the conflated processes of reading and writing.

CASE REPORT

The subject

The patient was a 58-yr-old woman with a high school education and 2 yrs of technical school training. She had been employed for several years as a technician and secretary in a civil engineer's office. Her job responsibilities included reading and reporting on official documents, proof-reading documents for typographical and other errors, typing, and basic calculations. She enjoyed reading novels, magazines, and a daily newspaper. She was fully right handed (+100 on the Geschwind-Oldfield questionnaire) and had no family history of left handedness. She presented to her local physician with complaints of word-finding problems and difficulty in typing. She had no complaints regarding reading or writing at this time. X-ray computed tomography (CT) of the head revealed a small lesion in the left frontal lobe. She subsequently underwent a left frontal craniotomy aimed at excizing a single metastasis from an adenocarcinoma of the lung located in the dorsal aspect of the left frontal region. The intervention was successful and required minimal surgical damage in the area. The postoperative course was uneventful. Another CT scan obtained 18 months after the operation revealed a stable surgical lesion (described below) and no evidence of recurrent intracranial tumour. Neurological evaluation was normal, other than for the cognitive defects described below.

The patient and her husband independently described a generally good postsurgical recovery without notable changes in thinking, memory, or behaviour. With the exception of rare paraphasias immediately after the operation and residual mild word-finding problems, speech and language comprehension was also reported to be normal. However, the patient complained of major impairments of reading and writing which had effectively eliminated those capacities from her daily life. She was especially distressed by the loss of her reading ability, as reading had been a favourite pastime. She was able to adapt more easily to the writing defect by clever means such as using a rubber stamp for her signature and drawing pictures for her shopping lists. Neither language therapy nor persistent self-teaching efforts at home resulted in any significant improvement of reading or writing.

Neuroanatomical study

The basic neuroanatomical study was based on analysis of CT images according to the standard procedures of our unit's Neuroimaging Laboratory (Damasio, 1983; Damasio and Damasio, 1989). The method calls for patient identification to be masked in all film transparencies, and for investigators blind to the patient's neuropsychological status to select an appropriate template system for plotting abnormal images, and chart the position of those images on a standard protocol. A transparency containing the boundaries of neural units of interest, in both grey and white matter structures, is then superimposed on the chart, and damage is assigned to the units that contain the abnormal images.

The basis for the results reported here was a CT obtained 18 months after surgery. It showed an area of low density in the left dorsolateral frontal lobe (fig. 1). The area of damage was seen in a high cut, superior to the level of the lateral ventricle. Analysis indicates it was located in the premoter region, in Brodmann's field 6, above Broca's area (Brodmann's fields 44 and 45), and immediately posterior to the lowest level of field 8. It did not extend into prefrontal cortices (fields 46 or 9).

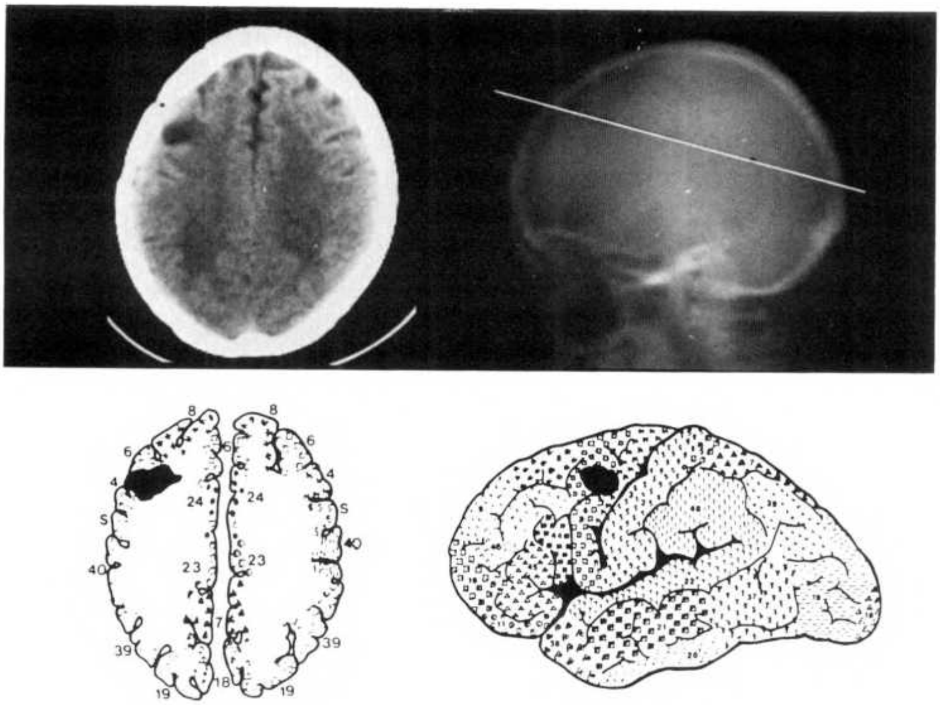

FIG. 1. *Upper*: CT scan obtained 18 months after surgery. The area of postoperative damage is seen in the left frontal lobe on one cut only (shown here). On the right side is a skull x-ray with the incidence for this cut. *Lower*: corresponding template showing the lesion in the left premotor cortex (Brodmann's area 6), immediately behind Brodmann's area 8, and well above Broca's area.

A special study was undertaken to check the reliability of the anatomical localization obtained by the standard template method. An independent method based on the stereotaxic method of Talairach (Talairach *et al.*, 1967) was used, drawing on information obtained from the patient's skull films and CT. The anatomical region identified by this method was the same (fig. 2).

Neuropsychological study

Neuropsychological evaluation was conducted 6 and 12 months postsurgery. The patient's abilities and impairments were almost entirely stable across epochs, and the findings have therefore been combined.

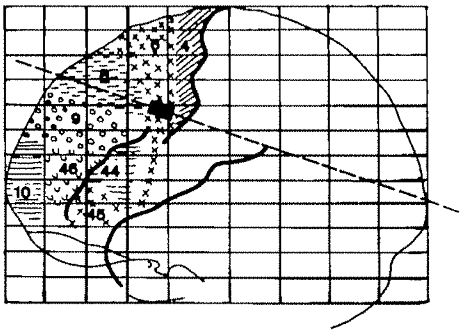

FIG. 2. Confirmatory reconstruction and plotting of the CT lesion using Talairach's method. The lesion is again localized to premotor cortex immediately behind the lower portion of area 8 and above Broca's area.

The exceptional limited recovery of some specific abilities which occurred between the first and second examinations is noted. A summary of the neuropsychological test data is presented in the Table.

Intellect and memory. There was no evidence of impairment of intellect or memory. Performances on selected subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) were in the average range and consistent with the patient's estimated premorbid abilities. Of particular interest with regard to her alexia and agraphia was the finding that she had no difficulty performing the Digit-Symbol Substitution subtest of the WAIS-R. She was able to discuss current news events and history without difficulty, and performances were within normal limits on tests of verbal memory (Wechsler Memory Scale; Lezak, 1983, p. 463) and visual memory (Benton Visual Retention Test; Benton, 1974).

Visual perception and visuoconstructional abilities. She performed at the 98th centile on Benton's Facial Recognition Test (Benton *et al.*, 1983), which is sensitive to deficits in visuoperceptual discrimination. As illustrated in fig. 3, drawings of common objects, such as a clock and a house, were normal. Copy of the Rey-Osterrieth Complex Figure (Lezak, 1983, p. 395) contained evidence of moderate spatial distortion, with a score of 27/36. Gestural praxis to copy and to dictation was entirely normal with both hands.

Cognitive abstraction and fluency. The patient obtained only one category on the Wisconsin Card Sorting Test (Heaton, 1981). Performance was defective (5th centile) on the Controlled Oral Word Association subtest of the Multilingual Aphasia Examination (MAE) (Benton and Hamsher, 1978). On a modified version of the design fluency test (Jones-Gotman and Milner, 1977), she produced 8 figures in 3 min, slightly below normal expectations (S. W. Anderson, unpublished results).

Speech and aural comprehension. Speech was fluent, well articulated, prosodic, and nonparaphasic. Volume and rate of speech were normal. There were occasional short pauses which the patient attributed to word-finding difficulty. Comprehension of conversational speech was normal. On the MAE, performances were normal on tests of visual naming, sentence repetition, oral spelling, and aural comprehension. In sum, there was no indication of aphasia.

Reading sentences and words. Performances were severely impaired on all administered tests of oral reading and reading comprehension. The patient reported that she was unable to extract any meaning from words which she was unable to say aloud, and that she could immediately and easily speak any printed word which she recognized. Consistent with this, performances on reading comprehension tests which did not require an oral response were severely impaired. She was correct on only 6 of 18 items on the MAE Reading Comprehension test, which requires matching a single printed word or short phrase to the correct picture in a multiple (4) choice format. This level of performance is below the first centile. Performance was also severely impaired on another reading comprehension task which required no oral response. She was presented with four categories of items (transportation, food, furniture, and animals), each symbolized by a line drawing of a representative item (automobile, apple, chair, and cat, respectively).

TABLE. STANDARDIZED NEUROPSYCHOLOGICAL TEST SCORES

Wechsler Adult Intelligence Scale—Revised

Estimated Verbal IQ: 97
Estimated Performance IQ: 86

Age corrected scaled score			
Information	11	Block design	8
Similarities	9		
Arithmetic	10	Digit symbol substitution	9
Digit span	11		

Wide Range Achievement Test—Revised

	Raw score	*Standard score*	*Centile*
Reading	17	51	0.08
Spelling	41	114	82
Arithmetic	30	97	42

Multilingual Aphasia Examination

	Score	*Centile*
Visual naming	59	75
Sentence repetition	14	83
Controlled oral word association	22	5
Reading comprehension	6	1
Oral spelling	10	40
Written spelling	0	1
Token Test	44	82

Boston Diagnostic Aphasia Examination

	Correct	*Errors*
Arithmetic	27	5
Reading sentences and paragraphs	0	10

Wechsler Memory Scale

		Raw score	
	Scaled score	*Immediate*	*30 min delay*
Paragraph recall	13.1	9, 9	6, 2
Paired associates	14.6	9-11-12	12

Benton Visual Retention Test

Number correct	6
Number of errors	5

Facial Recognition Test

Raw score	53
Centile	98

Rey-Osterrieth Complex Figure Test

Copy score 27 of 36

Wisconsin Card Sorting Test

Categories completed	1
Number correct	65
Number of errors	63
Perseverative errors	35

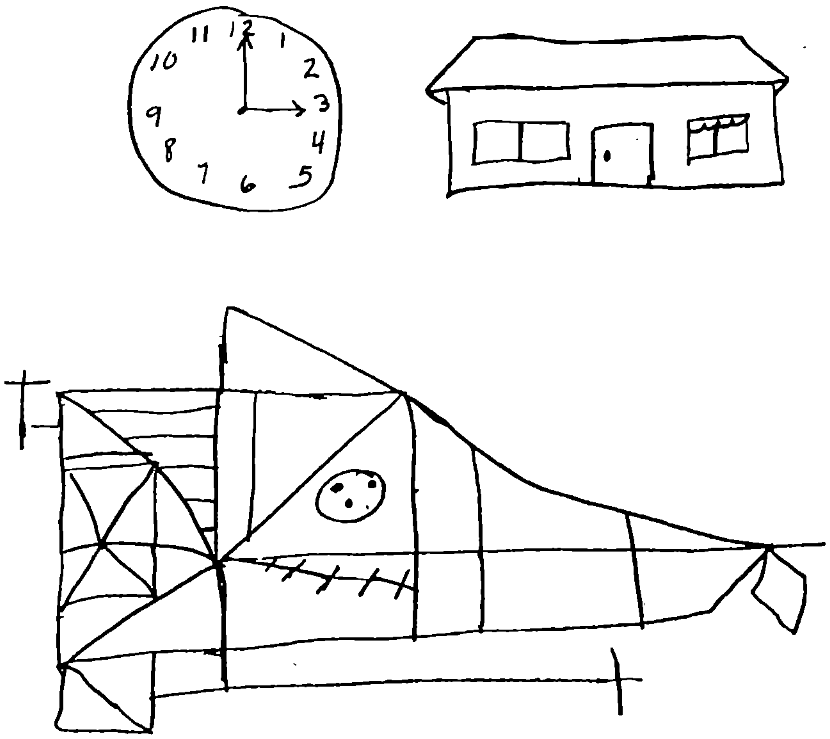

FIG. 3. Drawing of a clock and a house, and copy of the Rey-Osterrieth Complex Figure.

She was then asked to place each of 40 printed words, denoting 10 common objects from each category, into the appropriate category. She associated 20 of the 40 items (50%) with the appropriate category. Errors were evenly distributed across categories (6 transportation, 4 food, 5 furniture, and 5 animal). One additional reading comprehension test not requiring an oral response was administered. Following failure on the standard administration of the Reading Sentences and Paragraphs Test from the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass and Kaplan, 1972), she was asked to attempt to read silently the items and point to the appropriate response. She failed the first 5 items (the 2 examples and items 1–3), and the test was discontinued. Together, these findings clearly indicate that the alexia was not a defect in the spoken production of words which were appropriately perceived and comprehended, but rather an impairment of reading comprehension in the setting of normal speech production.

The patient was able to read aloud less than 21% (83/400) of all words presented to her. On the words which were not identified, she made very few paralexic errors (6 paralexic errors in 400 responses); a word was either immediately identified in a 'gestalt' manner, or she had no idea what it was. The paralexic errors which were made all involved the substitution of visually similar words (i.e., 'click' for CLICHE, 'house' for HORSE, 'stead' for STEAK, 'bacon' for BEACON, 'sleep' for SHEEP, and 'women' for WOMAN). On no occasion was she able to sound out phonemically an unrecognized word on any of the reading tests which were administered. She was completely unable to read pronouncable pseudowords such as ONT, FOO, and MUN (0 of 16 pseudowords correct on the Dyslexia Screening Test Short Form developed by Coltheart *et al.* (K. Patterson, personal communication, 1984)). In sum, the patient's word-reading ability consisted of the recognition of a limited number of words in their entirety, and there was a complete inability to identify words by means of grapheme to phoneme translation.

Stimulus characteristics in word reading

Four hundred printed words presented to the patient for her to read were coded for (1) number of letters, (2) frequency of occurrence in English reading material (Thorndike and Lorge, 1944), (3) imageability (Paivio, 1982), and (4) part of speech. Considering first the effect of word length, the words which were read correctly were shorter (mean length 4.98 letters, SD 1.87, range 2 – 10) than those not read correctly (mean length 5.99 letters, SD 2.12, range 1 – 12), t (143) –4.28, $P < 0.001$. Of the 225 words with 5 or fewer letters, 59 (26.2%) were read correctly, while only 13.7% (24/175) of those with 6 or more letters were read correctly.

The words which were read correctly also received higher frequency ratings on the 100-point Thorndike-Lorge scale than those words not read correctly. Frequency ratings were available on 384 words (82 read correctly, 302 not read correctly). Correctly read words received a mean frequency rating of 68.65 (SD 36.14, range 2 – 100) compared with a mean of 44.52 (SD 38.32, range 0 – 100) for those not read correctly, t (135) 5.29, $P < 0.001$. Words with frequency ratings of 50 or greater were read correctly on 30.4% (59/194) of the presentations, while those with frequency ratings less than 50 were read correctly on only 12.1% (23/190) of the presentations.

Imageability ratings were available on 146 words (42 read correctly, 104 not read correctly). The words which were read correctly were rated more highly imageable on Paivio's 7-point scale than the words which were not read correctly. The mean imageability rating for those words read correctly was 5.28 (SD 1.74, range 2 – 7), compared with a mean of 4.36 (SD 1.70, range 1 – 7) for those not read correctly, t (74) 2.90, $P < 0.005$. Of those words with imageability ratings of 5 or greater, 41.8% (28/67) were read correctly, compared with 22.9% (8/35) of words with imageability ratings of 3 or less. It should be noted that imageability was not correlated with frequency (r –0.077, P 0.177).

When the patient's performance on word reading was analysed for effects of part of speech, it was found that nouns were read correctly more often than any other grammatical category, with 24.7% (62/251) read correctly. Next were prepositions, with 15.4% (2/13) correct, and verbs, with 13.7% (7/51) correct. Performance was worst with adjectives, with only 9.9% (7/71) read correctly. Conjunctions, pronouns, proper nouns, adverbs, and articles were not presented in sufficient number to analyse.

Several of the words which were read correctly were often encountered by the patient on signs (e.g. STOP, EXIT, HOSPITAL, WOMEN), or letterheads (e.g. the words DEPARTMENT and RECREATION, which appeared on addresses and letterheads at her place of employment). On other occasions, there was no evident reason why a particular word was identified. For example, the patient identified only 8 words on the Reading subtest of the Wide Range Achievement Test-Revised (WRAT-R) (Jastak and Wilkinson, 1984), 7 of which were among the first and easiest words on the list. She then proceeded through the next 40 or so items, without being able to read a single word, until she came upon the word SEPULCHER near the end of the list. She read this word immediately, despite the fact that she was unable to recall having seen it recently or that it had any particular significance.

Reading letters. When letters were presented individually in large typewritten print, she was able to identify nearly 50% of them (54/112). Her errors frequently consisted of the substitution of visually similar letters, such as S for Z, and B for D. To determine if the impairment was limited to oral reading of letters, a cross-case letter-matching task was administered. Fourteen upper case letters were listed in random order in a vertical column and the 14 associated lower case letters were listed in a different random order in a second vertical column. The patient's task was to draw a line between each upper and lower case letter pair. Two pairs were completed by the experimenter while explaining the task. The patient was correct on 8 of the 12 remaining pairs. The correct matches were: R-r, E-e, L-l, N-n, T-t, O-o, C-c, and V-v. The mismatches were: D-c, P-d, S-z, and Z-s. She was 100% correct in the identification of very large (3 inch) block letters, and she also was able accurately to describe the shape of letters when no visual stimulus was present.

Reading numbers and symbols. In sharp contrast to her impaired word and letter-reading ability, the patient experienced no difficulty in reading single or multidigit numbers. Fifty numbers printed in large typewritten print, ranging from 1 to 7 digits, were read aloud without error. Complex numbers were read appropriately; for example, 3,245,619, was read as 'three million, two hundred forty-five thousand, six hundred and nineteen'. She had no difficulty identifying individual digits within a complex number, and she could readily state their place value. As evidenced by her preserved ability to perform written calculations (described below), she was able to understand complex configurations of numbers and arithmetic symbols. She was also 100% correct in the identification of 15 symbols commonly found on typewriters (e.g., %, ?, *, @).

Spelling. There was no impairment of oral spelling. She performed within normal expectations on two versions of the oral spelling subtest of the MAE (19/22 words correct, 40th centile, average range), and obtained a standard score of 114 on the WRAT-R spelling test when allowed to provide oral responses instead of the standard written responses. She was able to spell regularly and irregularly spelled words. When asked to introspect on the mental processes involved in her spelling ability, the patient noted that this task did not seem any more difficult than usual, and that she was able to form an internal image of the desired word and then 'read' the individual letters from the image. Eleven words (MAE Spelling Test List B) were orally spelled to the patient. She was able to identify 7 of these words, the longest of which contained 7 letters (TRAILER).

Writing letters and words. Consistent with the patient's description of writing difficulty, severe agraphia was evident on formal assessment. Representative samples of her writing are provided in fig. 4. Writing was slow and laboured, output was limited, and she displayed both intense concentration and frustration when attempting to write. Most attempts at writing even single letters ended with the patient giving up after several minutes without producing anything. Exceptions to this were infrequent, but on 15 occasions she did produce some form of written response when attempting to write single letters to dictation. All

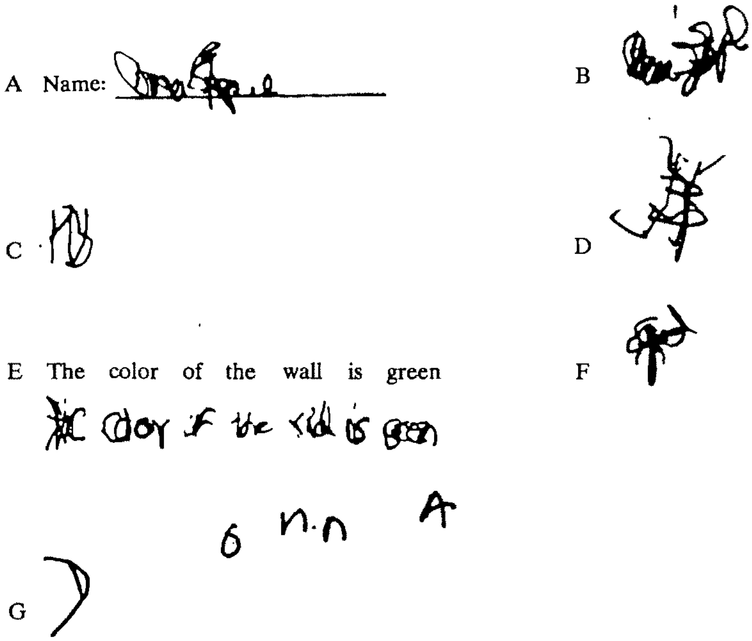
A Name:
B
C
D
E The color of the wall is green
F
G

FIG. 4. Seven representative samples of the patient's writing. A, her name; B, her name written with her eyes closed; C, the letters 'A' and 'B' written to dictation with the right hand; D, the letters 'A' and 'B' written to dictation with the left hand; E, writing to copy; F, the word 'DOG' written to dictation; G, her name, printed with her eyes closed and with the examiner moving the paper.

but 2 of the 15 letters were illegible (the letters 'X' and 'O' were legible). No legible words were written to dictation or spontaneously. When she produced a written response when attempting to write words to dictation, severe spatial distortion was evident. Graphemes were poorly formed and often not formed at all. There was often no link among graphemes to form a word—even her own name. On occasion, when individual graphemes within a word were legible, she failed to move sequentially to a new position in space so that the shapes of multiple graphemes became superimposed in an illegible scrawl. When deprived of visual guidance by a blindfold, her writing remained illegible. Writing was equally impaired with her nonpreferred left hand.

Writing to copy was defective at both 6 and 12 months postsurgery, although there was evidence of limited recovery between the two examinations. At the first evaluation, 62.5% (15/24) of the copied letters were identifiable, but letters within words were often overlapping. At the second evaluation, 100% (60/60) of copied letters were identifiable, although there continued to be evidence of mild spatial distortion and occasional overlapping letters within words.

It was observed that when the patient attempted to write her name, all or parts of the individual graphemes appeared to be present, but were produced on top of each other and in a spatially distorted fashion. She was instructed to attempt to write her name slowly while the examiner moved the paper to provide spacing within and between letters. She was at first overwhelmed by this task and produced nothing. She was then told to close her eyes and write her name slowly. The examiner moved the paper as previously and the result was an awkward, but legible, version of her name (fig. 4). This procedure was not successful with other words.

Writing numbers. In contrast to her severe agraphia, the patient was able to write single and multidigit numbers without difficulty. Writing of 2 to 5 digit numbers was performed without error to dictation (100% correct on 25 numbers) and to copy (100% correct on 15 numbers).

Written calculation. As shown in fig. 5, she was able to perform written calculations involving addition, subtraction, mutiplication, and division. Performance was at the 97th centile on the Arithmetic scale of the WRAT-R, and she was correct on 27/32 (84%) arithmetic problems from the BDAE. Errors occurred primarily on the most difficult tasks, which involved percentages, fractions, and long division. She noted that performing calculations seemed to be somewhat more difficult than it had been premorbidly, but she felt that her level of performance was essentially unchanged.

In sum, this patient had a stable neuropsychological profile characterized by severe alexia and agraphia in the setting of otherwise well-preserved linguistic and cognitive functions, and in the absence of motor defects. There was a striking dissociation between the severe impairment in the reading and writing of letters and words and her intact ability to read and write numbers and perform written calculations. This defect was associated with a circumscribed lesion in the left premotor cortex located above Broca's region.

DISCUSSION

Alexia and agraphia associated with damage to frontal cortices

To our knowledge, there is no previous report of alexia associated with frontal lobe damage in the absence of aphasia. On the other hand, damage to the left frontal lobe has long been associated with alexia in the setting of Broca's aphasia (Lichtheim, 1885; Déjerine and Mirallié, 1895; Nielsen, 1938, 1946). In fact, the finding that impairment of reading comprehension could be caused by purely anterior lesions quite distant from areas essential for visual perception and language comprehension has been used as evidence for the argument that language processes are nonlocalized within the left hemisphere (Freud, 1953; Marie, 1906). Benson (1977) reported that 51 of 61 patients (84%) with Broca's aphasia and no evidence of posterior lesions had at least mild alexia,

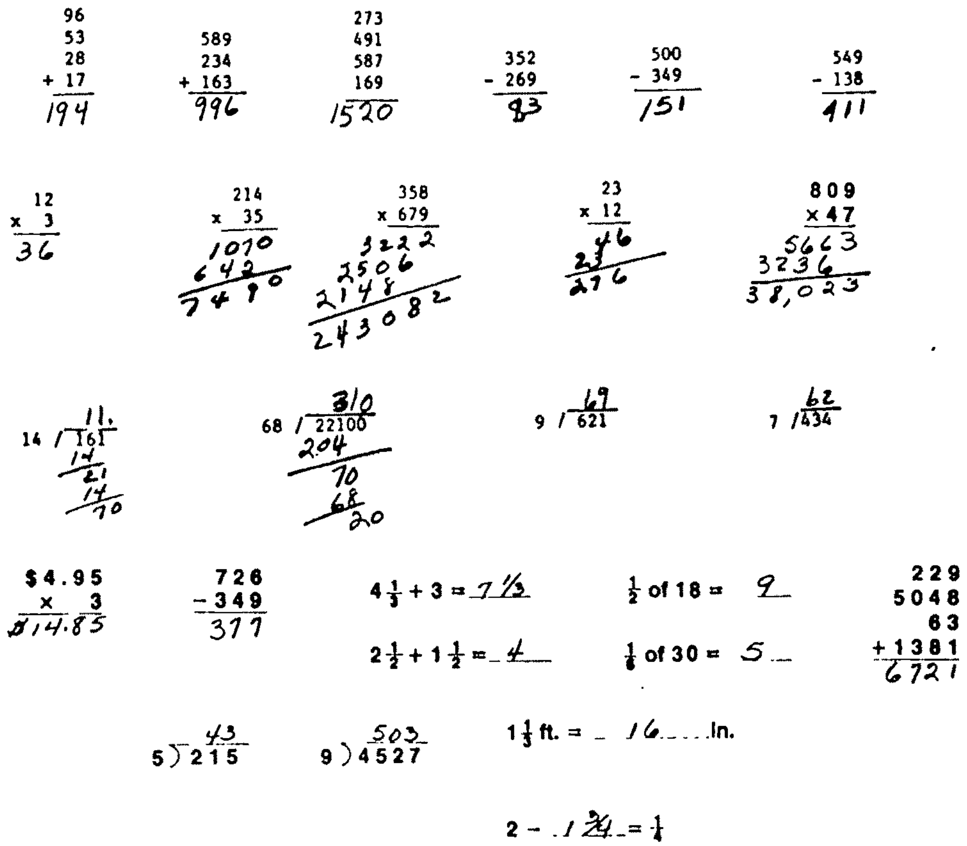
96 53 28 + 17 194
589 234 + 163 996
273 491 587 169 1520
352 - 269 83
500 - 349 151
549 - 138 411
12 x 3 36
214 x 35 1070 642 7490
358 x 679 3222 2506 2148 243082
23 x 12 46 23 276
809 x 47 5663 3236 38,023
14 / 161 11. 14 21 14 70
68 / 22100 310 204 70 68 20
9 / 621 69
7 / 434 62
$4.95 x 3 $14.85
726 - 349 377
4 1/3 + 3 = 7 1/3
2 1/2 + 1 1/2 = 4
1/2 of 18 = 9
1/6 of 30 = 5
229 5048 63 + 1381 6721
5) 215 43
9) 4527 503
1 1/3 ft. = 16 In.
2 - 1 3/4 = 1/4

FIG. 5. Examples of the patient's written calculations (items from the WRAT-R and BDAE).

and 34 of these patients (56%) had severe alexia. The alexia was characterized by a preserved ability to recognize some words in their entirety, even though individual letters within the word could not be identified, and no words could ever be decoded by means of grapheme to phoneme conversion. It has also been noted that oral reading and reading comprehension in Broca's aphasia may mirror the typical patterns of language breakdown in these patients, in that concrete nouns may be more likely to be read correctly than functor words such as conjunctions, prepositions, pronouns and articles (Gardner and Zurif, 1975; Kaplan and Goodglass, 1981; Friedman and Albert, 1985).

The appropriate study of agraphia associated with frontal damage has been hampered by the fact that lesions which cause interesting linguistic defects are also likely to cause motor impairment of the dominant arm and hand. Despite this confounding factor, three general types of agraphia have been associated with focal lesions of the left frontal lobe. Two of these types of agraphia occur in the setting of Broca's aphasia. They are an agrammatic agraphia (Marcie and Hécaen, 1979; Kaplan and Goodglass, 1981), in which graphemes and words are generally well formed, but written sentence structure is agrammatic, and an agraphia characterized by poor grapheme production and impaired spelling due to letter omissions and substitutions (Kaplan and Goodglass, 1981). The third type is usually characterized as a 'pure agraphia' because it occurs in the context of otherwise well-preserved linguistic abilities.

There have been a small number of cases of pure agraphia which point to an area of involvement in the left frontal cortex. Exner (1881) is usually credited with first describing agraphia in association with lesions of the superior aspect of the left premotor cortex, namely, the region above areas 44 and 45 (Broca's area), often referred to as 'Exner's area'. Nielsen (1946) noted that 'There is a writing center at the foot of the second convolution of the major side (first postulated by Exner, 1881) which is especially trained from childhood through the formation of engrams to function as a writing center in the functional sense.' (p. 40). Severe agraphia associated with a cyst in Exner's area was reported by Eskridge and Parkhill (1896). The agraphia was characterized primarily by poorly formed and omitted letters and spelling errors. Writing was described as extremely slow and laborious. The patient was not aphasic, and reading was relatively preserved, although it was noted that he 'not infrequently omits and miscalls words' (p. 124). Perhaps the best documented case to date of pure agraphia associated with a lesion in Exner's area was reported by Gordinier (1899). The patient, Lizzie W., presented with relatively isolated agraphia characterized by poor grapheme formation and perseveration. She did not have aphasia or hemiparesis, and reading was reported to be normal. The ability to write numbers and the ability to draw were not reported. Autopsy revealed a single small glioma located in Exner's area.

Other cases of agraphia associated with more extensive left frontal lobe damage have been reported. Penfield and Roberts (1959) described a patient who developed transient agraphia following an extensive excision of the second and third frontal convolutions below the level of Brodmann's field 8 in the left hemisphere. The patient's agraphia, which resolved within 3 months, was characterized primarily by agrammatism. During the period that the patient was agraphic, he was not aphasic, and reading was normal. Number writing and drawing were not described. Dubois *et al.* (1969) described 6 agraphic patients without major impairment of oral language, reading or praxis. Their agraphia was characterized by poor grapheme selection in the setting of relatively preserved grapheme formation and preserved oral spelling. These patients had acalculia and impaired number writing. Four of these patients were presumed to have frontal lobe damage, but precise anatomical information was not available. More recently, a patient with agraphia associated with a focal lesion of the left precentral gyrus, immediately posterior to Exner's area, was described by Rapcsak *et al.* (1988). Despite the fact that the lesion was confined to the motor cortex, motor strength was normal. The patient's agraphia was characterized as a lexical agraphia, that is, letters were well formed, but written spelling of irregular words was impaired relative to spelling of regular words and orthographically regular nonwords. The patient was not alexic, but oral spelling mirrored the pattern of written spelling.

It is evident from these reports that damage to aspects of the left frontal cortex may impair both reading and writing. However, due largely to the scarcity of cases not confounded by aphasia and/or hemiparesis, many questions remain unanswered regarding the neuroanatomical basis and cognitive mechanisms underlying these defects. In the present case, CT did not reveal any lesion other than the circumscribed left frontal lesion described above. This was true for all studies, including the one obtained 6 months after the last neuropsychological examination. Although we cannot entirely exclude the possibility of other lesions undetected by CT, it is important to note that there was no suggestion from the neurological or neuropsychological evaluation that additional brain areas were damaged. Furthermore, a sample of writing obtained immediately before the frontal craniotomy showed mild perseveration but was otherwise normal. The patient denied any difficulty reading before surgery.

Mechanisms underlying alexia and agraphia associated with frontal damage

Unilateral dorsolateral damage to the frontal lobe often results in a residual gaze paresis (when area 8, the eye field region, is involved), which limits eye movements to the side opposite the lesion and renders them uneven. Weak or poorly coordinated eye movements from left to right would clearly impede normal scanning of a sequence of graphemes, and this is possibly a factor in some cases of alexia associated with frontal damage. In the present case, however, several lines of evidence indicate that this patient's alexia cannot be attributed to a simple scanning defect. She was unimpaired in the scanning of digit sequences and equations, and she was able to scan unfamiliar faces without difficulty on Benton's test of visuoperceptual discrimination. Her performance was within normal limits on the Digit-Symbol Substitution subtest of the WAIS-R. In addition, she was severely impaired in the identification of single letters, a task which should not be affected by a scanning defect.

Consistent with Benson's (1977) description of alexia associated with Broca's aphasia, this patient could infrequently recognize a word in its entirety. The pattern of reading disturbance resembled a severe form of 'phonological alexia' described by Beauvois and Dérouesné (1979), in that high frequency words were more likely to be read correctly than low frequency words, there was a complete inability to read pseudowords, and all paralexic errors were 'orthographic paralexias' (Friedman and Albert, 1985), that is, words were misread as orthographically similar words. Additionally, the probability of word recognition increased for words which were short, highly imageable, and nouns. Various manifestations of phonological alexia have been described by others (e.g., Casey and Ettlinger, 1960; Marshall and Newcombe, 1973; Friedman, 1982), and have been interpreted in the context of models of reading comprising two partially independent reading comprehension processes (Marshall and Newcombe, 1973). The phonological route involves individual grapheme to phoneme conversion prior to lexical activation, and is evidenced in the normal reading process of 'sounding out' unfamiliar words. The route thought to be used most often by normal readers does not involve grapheme-phoneme conversion, but rather the global identification of words, phrases, or word fragments. The present case provides further evidence for dissociation of these two routes to reading comprehension at cognitive and neural levels. Although both systems were severely impaired, there was relative preservation of the global identification of words, with no indication that the phonological route was functional.

Of particular interest in this case was the finding that the alexia was defined in part by the knowledge domain to which the stimulus belonged, namely, the impairment pertained to words and letters, but not to stimuli that are, from a physical structure standpoint, visually comparable. This impairment was not due to a loss of knowledge about those entities. She was able to describe the shape of letters, their phonemic representations, and their role in the spelling of specific words. Nor was her alexia due to nonspecific impairment of visual perceptual discrimination. Instead, the visual information derived from attending to a grapheme or word failed to lead to the coactivation of the semantic value of that information. To all intents and purposes, this impairment should be conceptualized as a domain–specific visual recognition defect, in that she was unable to identify or derive meaning from individual members of a particular category of entities. We will argue below that a common mechanism underlies both this defect and her agraphia.

In the present case, the predominant feature of the agraphia was severely defective grapheme formation. There was no indication that the repertoire of movements required for writing was disturbed. The finding of limited spatial distortion in her copy of a complex geometric figure was the only indication that this impairment was not confined entirely to the domain of letters. Spatially distorted grapheme production in association with relatively preserved drawing has been previously described in association with ipsilateral parietal damage (Roeltgen and Heilman, 1983), contralateral parietal damage (Margolin and Binder, 1984), and left parieto-occipital damage which extended through the corpus callosum to the right hemisphere (Baxter and Warrington, 1986). In the present case, when the patient produced graphic symbols of nonletter domains she presumably was using all the movements that are required for writing graphemes. Why should she succeed with one domain and not another? Our proposal is that the precise sequence of movement components as well as the context in which they are produced are different for the graphic verbal domain and the graphic number domain. Considering that the motor patterns necessary to produce both letters and numbers are decomposable on geometry-based fragments, we suggest that it is the sequence of fragments (their combinatorial arrangement) and the overall context of performance that set the stimuli apart and define the domains to which they belong. The severe impairment in writing letters and words may thus be conceptualized as a highly specific impairment of visuoconstructional ability, which pertained only to the domain of graphemes and words.

In this regard, it is pertinent to note that lesions involving frontal association cortices in nonhuman primates may result in impairment of behaviours requiring complex motor sequences, such as defective ordering of a series of movements (Deuel, 1977). In addition, the study of apraxia in humans led to the postulation that premotor cortices are involved in the integration of fragments of motor sequences which must be activated together to produce complex purposeful movements (Paillard, 1982).

Alexia and agraphia: separate or joint defects?

It is possible that alexia and agraphia in this patient were independent impairments that followed damage in two separate but contiguous neural systems subserving reading and writing. It is also possible, and we believe probable, that the two defects are based on the disruption of a neural unit that participates in both reading and writing.

There are reasons to believe that the alexia and agraphia of this patient shared a common basis. First, it is improbable that *only* reading and writing, two processes closely linked in development and behaviourally related, would be impaired in the setting of otherwise well-preserved cognitive abilities, due to concomitant damage to independent but contiguous neural structures, caused by such a small lesion. Secondly, the degree of similarity between the pattern of reading impairment and the pattern of writing impairment also suggests common underlying mechanisms. Alexia and agraphia had a comparable degree of severity, and both were defective at the single letter level. The alexia and agraphia also shared a sharply demarcated boundary relative to domain, with both reading and writing of numbers being well preserved. Furthermore, the pattern of alexia closely resembled that reported in prevous cases of alexia *with* agraphia, and was distinct from that found in pure alexia: there was a complete breakdown of the ability to convert graphemes to phonemes, in spite of relatively preserved global word recognition, and reading of nouns was better than reading of other parts of speech (Gardner and Zurif, 1975).

Despite all of the factors pointing to a shared neural basis, the possibility that the alexia and agraphia in this case were independent defects cannot be excluded. Consistent with this view is the fact that alexia may occur in the absence of agraphia (e.g. Déjerine, 1892; Geschwind, 1965; Greenblatt, 1973; Damasio and Damasio, 1983), and vice versa (e.g., Exner, 1881; Gordinier, 1899; Dubois *et al.*, 1969; Assal *et al.*, 1970). Be that as it may, the significance of the case does not rest on the alexia and agraphia being related defects.

If the two defects are deemed independent, this patient would represent, to the best of our knowledge, the first reported instance of 'pure' alexia arising from a frontal lobe lesion. An anatomical basis for pure alexia in the paraventricular white matter of the left occipital region disrupting both interhemispheric and intrahemispheric visual pathways has been well established (Déjerine, 1892; Geschwind, 1965; Greenblatt, 1973; Damasio and Damasio, 1983), but explanation of the defect in terms of disrupted visuoverbal processing clearly does not suffice for alexia arising from frontal lobe damage. It is not surprising that a multifaceted learned behaviour such as reading may be disrupted at different points and by different neural/cognitive mechanisms, but the issue remains to define the possible role of areas within the left frontal cortices in the reading process.

Curiously, although we would not endorse the physiological mechanisms embodied in the thinking of Exner or Nielsen, it appears that the sector of association cortex known as 'Exner's area' is unquestionably related to the ability to write. Even more curiously, it also appears to be related to reading. It may be that this region plays a role in the coactivation of appropriate sequences of movements necessary to generate graphemes. The same neural units that could coactivate movement sequences would also coactivate fragmentary sensory memoranda in visual and auditory cortices uniquely associated with the graphemes, for example, both motor sequences to create the letter 'b' and the acoustic and visual patterns that pertain to it would be simultaneously coactivated. Clearly, the semantic value of 'b', its meaning, is derived from the experience of its associated sensory patterns (acoustic and visual). The hypothesis here is that, as a result of the early and concomitant learning of sensory descriptions of letters and associated graphomotor patterns, the neural network embodying 'letter knowledge' would conjoin sensory and motor representations. This would account for the presence of both reading and writing defects in relation to one single lesion over a neural region apparently more related to motor performance than to sensory operations.

The fact that this isolated and combined reading/writing defect has not been reported in relation to damage in the left frontal cortices is not surprising. Circumscribed lesions of the region damaged in this patient are infrequent. In our neuroanatomical records of over 1200 cases, we have only 4 other cases with damage limited to the superior aspect of the left premotor area. All were the result of stroke. Three of the cases had agraphia and 2 had alexia in the acute phase. In the chronic phase, the reading and writing of 2 of these patients had returned to normal. One case was seen only in the chronic phase, at which time no impairments of reading or writing were noted. The finding of alexia and/or agraphia in 3 of the 4 cases with anatomically comparable lesions supports the notion that this brain area participates in reading and writing. Several factors may have contributed to the finding that the stroke cases studied in the chronic phase did not manifest alexia and agraphia, including (1) differences in the pathophysiological properties and recovery from damage caused by a metastasis and surgical intervention as against that caused by stroke, (2) differences between cases in the specific location of the damage within the superior premotor region, and (3) possible individual differences in underlying neuroanatomical organization and/or differences in the functional mapping of reading and writing processes.

Alexia and agraphia typically occur in patients with larger lesions in the left frontal cortex that involve both the area damaged in the present case as well as cortex located inferiorly. Such lesions also cause aphasia, hemiparesis and acalculia. Perhaps the more restricted lesion in the present case simply points with greater precision to frontal cortex more critically involved in the reading/writing process.

Assuming that this anatomical area is involved in reading and writing, it remains to be explained why graphomotor patterns that appear entirely similar and certainly overlapping, namely, the patterns necessary to design numbers, are not at all compromised in this patient. And, likewise, why the reading of that other domain of stimuli, numbers, is preserved when so much of the physical structure of numbers that can be appreciated by vision clearly overlaps with that of letters. Previous research suggests that impairments of number reading, number writing and calculation typically accompany alexia and agraphia, although exceptions have been noted (Henschen, 1925; Hécaen *et al.*, 1961; Marcie and Hécaen, 1979). The similarity of the visual physical characteristics of numbers and letters, together with the fact that impairments of reading and writing usually co-occur across the two domains, point towards a shared neural substrate. However, as evidenced by the nearly complete dissociation in this patient, the representation of the domain of graphemes and the domain of numbers are, at least in part, separate and tied to separate neuroanatomical loci. It may be that in spite of physical structure overlap, the basis of the difference lies with the different motor sequences necessary to assemble letters and numbers out of component graphemic fragments. Even if design patterns get repeated, the order in which the local structural subcomponents of a design get to be entered in the global pattern of a letter or number would individualize letters and numbers as independent categories. In considering developmental factors which may be involved in this neural dissociation, it is interesting to note that number concepts appear to be typically acquired in strong association with the digits of the hand, possibly contributing to a neural substrate which is partially independent of that of letters and words.

Recent neuropsychological investigations have indicated that the organization of knowledge in both cognitive and neural forms may reflect categories of sensory stimuli and motor patterns (Warrington and Shallice, 1984; Damasio *et al.*, 1986; Goodglass *et al.*, 1986; Warrington and McCarthy, 1987; Damasio *et al.*, 1988). The findings in this patient provide further evidence for the dissociation of cognitive processes along lines of demarcation which correspond to the organization of specific knowledge domains.

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VISUAL CONTROL OF BALANCE IN CEREBELLAR AND PARKINSONIAN SYNDROMES

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SUMMARY

The role of vision in the control of balance in patients with Parkinson's disease (PD) and cerebellar disease (CD) was studied by measuring body sway with eyes open, closed, and in response to visual stimuli generated by discrete lateral displacements of a moveable room which enclosed the subjects. In response to room movement, normal subjects swayed by an amount intermediate between sway with eyes open and eyes closed and their response attenuated on repetition of the movement, a process depending on shifting from predominantly visual to proprioceptive control. CD patients swayed more than controls with eyes open or closed and as shown by high 'Romberg quotients' (eyes closed/eyes open sway ratio) were able to use visual information to control much of their unsteadiness. CD patients had a normal attenuation of response to repetition of the room movement. PD patients had normal sway with eyes open or closed but their responses to room movement were abnormal, being proportionately larger and failing to attenuate during successive stimuli. The results indicate that cerebellar lesions seem largely to spare the visuopostural loop and also spare the ability to shift from a visual to a proprioceptive control of postural sway. In contrast, the findings in PD suggest that the visuopostural loop is hyperactive and that its influence cannot easily be de-emphasized when visual information is misleading. The latter finding suggests that basal ganglia participation in posture is concerned with the reweighting of the various sensorimotor loops controlling posture in the process of adapting to novel situations.

INTRODUCTION

Postural control relies on sensory information from the vestibular, proprioceptive and visual systems. Although balance control is clearly abnormal in patients with Parkinson's disease (PD) and cerebellar disease (CD), the visual control of postural reactions has received little attention (Dichgans *et al.*, 1976). More generally, it is only recently that the specific role of vision in balance control has begun to emerge.

Studies of visuopostural control have sought to influence body sway either by manipulating the information content from the surrounding static visual environment (Bles *et al.*, 1980; Paulus *et al.*, 1984, 1987) or by moving visual stimuli (De Wit, 1972; Lee and Aronson, 1974; Lee and Lishman, 1975; Lestienne *et al.*, 1977; Nashner and Berthoz, 1978; Soechting and Berthoz, 1979; Lee, 1980; Talbott, 1980; Talbott and Brookhart, 1980; Bles *et al.*, 1983; Clément *et al.*, 1985; Bronstein, 1986). The concepts fundamental to our study can be credited in particular to Lee and coworkers

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who recorded visually-induced body sway in normal subjects standing inside a 'swinging room'; they reported that ' . . . oscillating the experimental room through as little as 6 mm caused adult subjects to sway approximately in phase with this movement. The subjects were like puppets visually hooked to their surroundings and were unaware of the real cause of their disturbance' (Lee, 1980). This observation conveys three significant concepts, first, that sway control follows a hierarchical organization where visual cues override vestibular and proprioceptive ones (' . . . visually hooked . . . ') secondly, that visuopostural reactions are directionally specific (' . . . in phase . . . ') and, thirdly, that this process is to a large extent automatic and subconscious (' . . . unaware . . . '). Similar studies in dogs have shown that the efficiency of the visuopostural loop increases dramatically when there is a conflict between visual and vestibuloproprioceptive cues, in this case during simultaneous oscillation of the floor and room at nonharmonically related frequencies (Talbott, 1980; Talbott and Brookhart, 1980). On the other hand, visually evoked postural responses rapidly habituate if the subject becomes aware that the visual frame of reference is moving and he has reliable proprioceptive information from the lower limbs (Bronstein, 1986). It is evident, therefore, that the influence of vision on posture is under continuous CNS regulation.

Cerebellar and basal ganglia lesions are known to have profound effects on balance reactions and it is reasonable to postulate that they participate in this central regulation of visuopostural reactions. In addition, clinical investigations suggest that the study of visuopostural responses in PD and CD patients may have particular relevance to an understanding of the factors underlying their unsteadiness. For instance, eye movement studies on smooth pursuit and vestibulo-ocular reflex suppression suggest a derangement of peripheral retinal information processing in these two conditions (Hood and Waniewski, 1984) and PD patients show an unusually high dependence on visual information for the execution of motor acts (Flowers, 1976; Cooke *et al.*, 1978), a feature frequently observed in clinical practice (Martin, 1967). The present study was undertaken in order to compare the effects of visual stimuli on balance in these two syndromes in order to clarify the different roles that the cerebellum and the basal ganglia play in visuopostural control.

MATERIAL AND METHODS

Eighteen patients with a clinical cerebellar syndrome were studied, all with CT or MRI evidence of cerebellar lesions; mean age was 49 (range 25–70) yrs. Some patients had additional (noncerebellar) mild neurological signs. Patients with clear abnormalities of vibration or position sense were not included since they are known to be intrinsically abnormal on visuopostural tests. The commonest diagnosis was primary cerebellar degeneration (8 patients), tumours (3 patients; 1 medulloblastoma, 1 haemangioblastoma, 1 metastatic), vascular lesions (3 patients; 2 probable infarcts and 1 haematoma), multiple sclerosis (2 patients), a patient with an almost pure cerebellar form of Wilson's disease and another with cerebellar ectopia. From a clinical point of view the patients were classified into (1) midline (vermis) ataxia if they had predominantly gait/trunk ataxia with abnormalities of slow-phase eye movements (3 patients with a cerebellar degeneration, 2 with infarcts and 1 with a medulloblastoma); (2) neocerebellar ataxia, with predominantly limb involvement (1 patient with a haemangioblastoma) and (3) diffuse ataxia, a combination of (1) and

(2) (5 patients with a cerebellar degeneration, 2 with MS and 1 each with a cerebellar haematoma, cerebellar ectopia, a metastatic tumour and Wilson's disease). There were no patients with afferent (spinocerebellar) ataxia or with predominantly anterior cerebellar lobe involvement.

There were 13 PD patients, mean age 59 (range 38–77) yrs; 3 of these had additional neurological findings not typical of idiopathic PD but no firm alternative diagnosis was ascribed. Two PD patients were untreated, the remainder were taking standard antiparkinsonian drugs. All patients entering the study could stand and walk unaided but were otherwise unselected. All had symptoms and signs at the time of the posturographic examination. The results for the PD patients were compared statistically with a group of 17 normal subjects with a mean age of 63 (range 38–74) yrs, and those of the CD patients with a group of 29 normal controls (including the 17 referred to above) with a mean age of 48 (range 19–74) yrs. The Mann-Whitney U test and the Wilcoxon rank W test in the SPSS/PC+ V2.0 statistical package (SPSS Inc.) were used with a significance level set at $P < 0.05$.

The displacement of the centre of force of the body was measured by means of a sway platform. The platform, earth-fixed, was placed inside a moveable room, measuring 2.50 m long, 2.20 m high and 1.80 m wide, mounted on pneumatic wheels (fig. 1). The room was displaced smoothly and quietly by hand. Its walls and ceiling consisted of a red and pink chequered fabric attached to the room's frame. The subject stood facing one of the lateral walls at a distance of 38 cm so that movement of the room produced full-field linear optokinetic stimulation along the interaural (y) axis. The stimuli consisted of discrete movements of the room, with a sigmoid time course, lasting approximately 12 s, over a fixed distance of 30 cm with a peak velocity of 2–3 cm/s (average peak angular velocity at the level of the eye = 3.76 deg/s). Three to 5 motion stimuli in each direction were delivered. Each stimulus consisted of motion of the room rightward (or leftward) from rest and then stopping. For the subsequent stimulus the room moved similarly in the return direction. The interval between stimuli varied between 8 and 16 s. Room displacement was monitored with a potentiometer attached to one of the wheels. All subjects were informed that the room would move and that the platform would not, and were encouraged to keep a natural upright posture. Prior to visual stimulation, spontaneous body sway was recorded with the subjects standing inside the stationary room with eyes open for 1 min and then with eyes closed for a further 1 min.

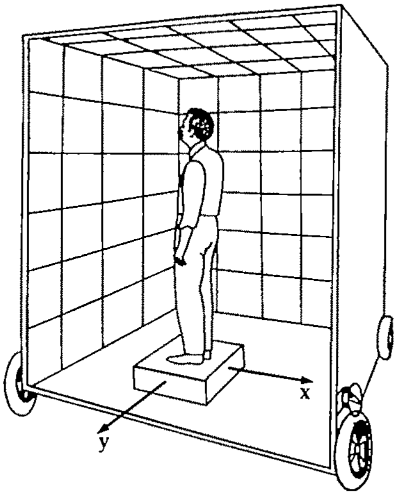

FIG. 1. Drawing to illustrate the procedure used to generate visually-induced body sway. The proximal wall of the room is cut away to show the interior arrangements. The room was displaced along the y axis while the subject stood on an earth-fixed sway platform. Sway path along the y axis was measured by computer.

Body sway in the coronal and sagittal planes plus the room displacement signal were recorded on paper with an ink jet polygraph and on magnetic tape for off-line analysis as follows. Sway path along the y axis was measured over periods of 12 s, using a computer program similar to that described by others (Hufschmidt *et al.*, 1980). In brief, the force signals from the subject standing on the platform were normalized to represent the force exerted by a 70 kg mass. During body sway the signals from the platform behave as if the force is moving across the surface of the platform. The computer program samples the momentary position of the centre of force and sums differences between successive positions to calculate the total length of the sway path. Measurements were carried out on a minimum of 4 periods with eyes open, 4 with eyes closed, and during all room displacements. These measurements were aimed at determining the overall instability of the subjects under the various experimental conditions, regardless of the amplitude/frequency content of body sway. However, a complementary measurement of sway frequency was undertaken in the PD patients to evaluate the possibility of selective effects of the experimental conditions on their limb tremor, transmitted to the force platform. This will be described in the relevant Results section.

RESULTS

Fig. 2 shows typical raw recordings of lateral sway in response to the first two room displacements in a normal control and in a PD and a CD patient. In each example the first stimulus was from left to right, as shown in the bottom trace; the sway recordings corresponding to the second stimulus (from right to left) have been inverted for ease of comparison. It can be seen that the normal response to the first room displacement

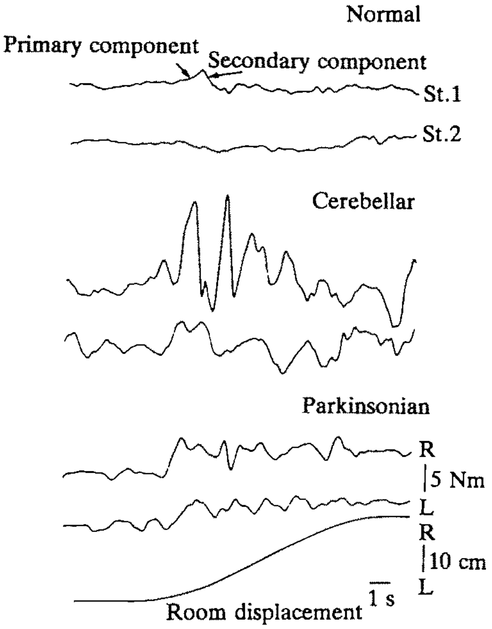

FIG. 2. Raw recordings of lateral body sway in response to the first (St.1) and second (St.2) displacement of the room. The first stimulus travelled from left to right and the second from right to left; the sway record during St.2 has been inverted in all subjects shown to facilitate visual comparison with St.1. Note, in the normal subject, the absence of the primary-secondary components of visually-induced body sway during St.2. The cerebellar patient, in spite of his marked baseline unsteadiness, also managed to attenuate considerably the visually-induced body sway during St.2. The parkinsonian patient had similar unsteadiness during St.1 and St.2 with a permanent shift of baseline sway in the direction of room motion.

consists of an initial sway (displacement of the centre of force of the body) in the same direction as the stimulus at a latency of approximately 800 ms (primary component). This was followed by a fully corrective displacement in the opposite direction (secondary component) and finally by some general unsteadiness. During the second stimulus the important finding is that the primary and secondary components are virtually absent, with only some slight nonspecific unsteadiness persisting. More detailed examination of the normal response can be found in an earlier publication (Bronstein, 1986); however, it is important to note that the discrete low velocity stimuli used in our studies do not provoke a tonic bias of posture as reported by authors using constant, high velocity stimuli (Dichgans *et al.*, 1976; Lestienne *et al.*, 1977; Clément *et al.*, 1985).

In the CD patient this pattern of response and attenuation is preserved, notwithstanding the pronounced spontaneous unsteadiness shown by this subject (fig. 2). In contrast, the recordings from the PD patient show that the amplitude of the primary component relative to his background sway is greater than normal, the secondary component is minimal such that the centre of force of the body remains displaced in the direction of the stimulus and, more importantly, the response is only marginally attenuated during the second stimulus.

Since the identification of these specific components of visually-induced body sway cannot always be distinguished objectively from the spontaneous body sway, and since sway path measurements have been shown to parallel closely those of the amplitude of the primary component (Bronstein, 1986), the data from all the subjects can be conveniently presented in terms of sway path. These results in the group of older normal controls, PD and CD patients are illustrated in fig. 3 which presents the mean of 4 or 5 combined measurements for each subject during eyes open, eyes closed and during visual stimuli, excluding the first room movement. This figure shows that CD patients

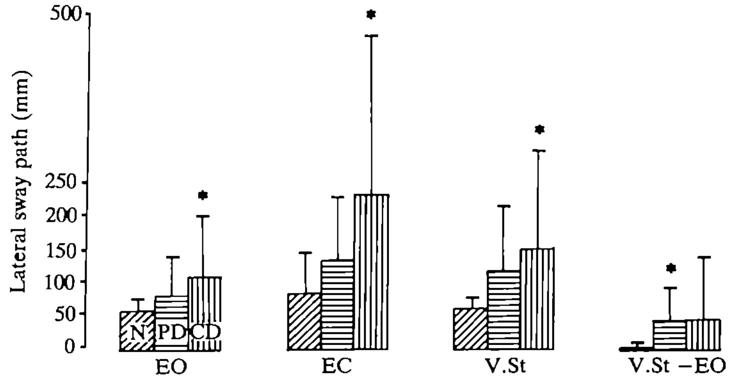

FIG. 3. Lateral body sway in older normal controls (N), parkinsonian (PD) and cerebellar (CD) patients recorded with eyes open (EO), eyes closed (EC) and during the visual stimulus of room displacement (V.St). The amount of body sway attributable to the room movement was estimated by subtracting sway with eyes open from sway during room motion (V.St−EO). The vertical bars indicate 1 SD. The asterisks indicate a statistically significant difference ($P < 0.05$) between the patients and their age-matched normal control groups.

swayed significantly more than controls with eyes open ($z = 3.02$, $P < 0.01$); closed ($z = 3.61$, $P < 0.01$) and during visual stimulation ($z = 3.21$, $P < 0.01$). All groups of subjects were significantly more unsteady during room movement than during spontaneous body sway with eyes open (older normal controls: $z = 2.67$, $P < 0.01$; all normal controls: $z = 3.51$, $P < 0.01$; PD patients: $z = 2.48$, $P = 0.01$; CD patients: $z = 2.11$, $P = 0.03$). This indicates that in all groups of subjects, regardless of their baseline sway and diagnosis, room motion has an unstabilizing effect.

An estimate of the sway due to the visual stimuli was obtained by subtracting sway with eyes open from sway during visual stimulation (*see* fig. 3, V.St−EO). PD patients had significantly higher V.St−EO values than normal controls ($z = 2.13$, $P = 0.03$). Despite having mean values considerably larger than normals, CD patients did not differ statistically from normals ($z = 1.20$) because of a much larger variance. An additional statistical analysis was carried out to assess the effect of visual stimulation by comparing the amount of sway during room motion with the condition of greatest instability, i.e., eyes closed. Older normal controls ($z = 2.10$, $P = 0.03$), all normal controls ($z = 2.08$, $P = 0.03$) and CD patients ($z = 2.67$, $P < 0.01$) swayed more during eyes closed than during visual stimulation. PD patients, however, were as unstable during visual stimulation as during eyes closed ($z = 0.35$; note the similar levels of sway obtained during eyes closed and visual stimuli in PD patients shown in fig. 3). These analyses indicate that room motion has a comparatively stronger effect on the PD patients.

Fig. 4 shows the ratio sway path with eyes closed/sway path with eyes open (EC/EO), often referred to in the literature as 'Romberg quotient' (Diener *et al.*, 1984) because it quantifies the contribution of vision to static balance. Patients with CD disease had significantly higher 'Romberg quotients' than normal controls ($z = 2.16$, $P = 0.03$).

The ratio sway path during the second visual stimulus/sway path during the first visual stimulus (*see* fig. 4, second V.St/first V.St) quantifies the adaptive process by which, in normal circumstances, the unstabilizing effect of room movement is rapidly suppressed, as exemplified in fig. 2. Most normal controls and CD patients had values below unity whereas PD patients had values significantly higher than normals ($z = 2.11$, $P = 0.03$),

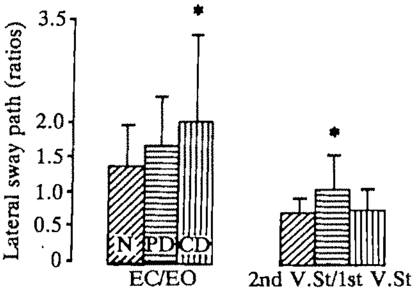

FIG. 4. Contribution of vision to static balance (EC/EO ratio or 'Romberg quotient') and proportional reduction in body sway during second room displacement with respect to the first one (i.e., ratio of second V.St/first V.St). Same symbols as in fig. 3.

implying a diminished ability to suppress the effects of a second visual stimulus in the PD group.

The possibility that the reduction in this adaptive property in PD patients might be related to the increased dependence on visual information described in this condition was examined. Fig. 5 shows the result of plotting the ratios second/first visual stimulus against eyes closed/eyes open, together with a regression line fitted to the data. Normal subjects and CD patients showed no association between these two variables whereas in PD there was a significant positive correlation (Pearson's r = 0.77, $P < 0.01$). Statistical confirmation of this trend in the PD group was obtained by additional analysis which included a nonparametric test of association between the two variables (Kendall's tau = 0.38; $P = 0.03$) and Pearson's r excluding an outlier with a second/first ratio higher than 2 (r = 0.55, $P = 0.03$). This finding indicates that PD patients who had a higher dependence on vision for postural stabilization, i.e., with a high 'Romberg quotient', were less able to suppress the effect of the second destabilizing visual stimulus.

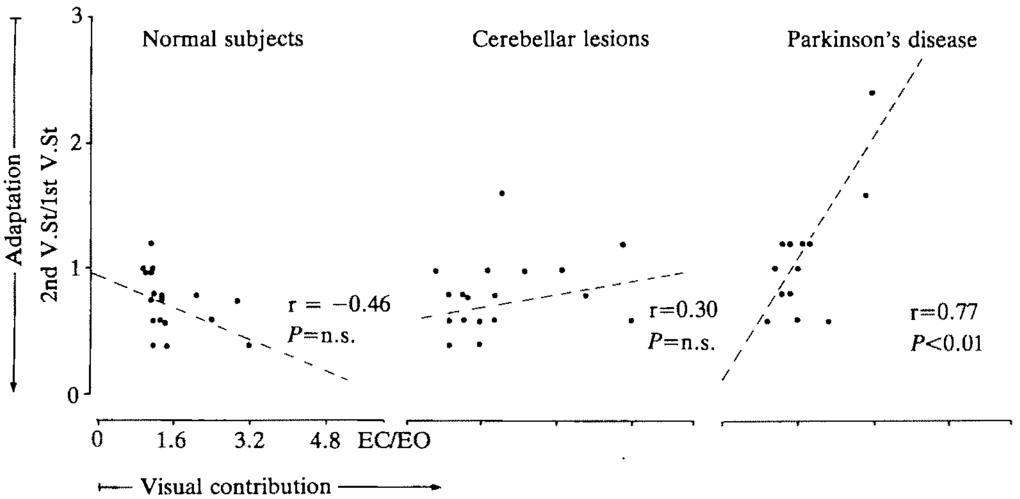

FIG. 5. Scatter plot showing the relationship between the amount of visual contribution to static balance (EC/EO) and the ability to attenuate body sway during a second room movement with respect to the first one (second V.St/first V.St) in the older normal subjects and in the patients. Regression lines, Pearson's r and significance values are shown.

A separate analysis was applied to the recordings from the PD patients, in order to quantify the influence of parkinsonian tremor on the results described above. The lateral sway records from each PD patient were subjected to Fourier analysis with a Solartron 1200 signal processor set with a baseband between d.c. and 100 Hz and a frequency resolution of 0.1 Hz. Periods of 12 s with eyes open, eyes closed and during room movement were measured. The power (V^2) in the band between 0.2 and 3 Hz and the power at the highest peak of the tremor, as identified on the power spectrum, were computed.

The power spectrum measurements in the 4 PD patients in whom a peak of tremor was identified, as illustrated in fig. 6, are presented in the Table. The contribution of the tremor to the total power was very small in 3 cases with tremor at about 6 Hz, although in the case with a 4 Hz tremor (illustrated in fig. 6) the tremor frequencies generated power of about 25% of that present in the lower frequencies. The Table also presents the results of the ratio second/first visual stimulus, as obtained by power spectrum and by sway path measurements, showing good general agreement between these two measurements. These 4 PD patients had ratios second/first visual stimuli below unity, that is, indicative of preserved ability to reduce sway during second presentation of the room movement.

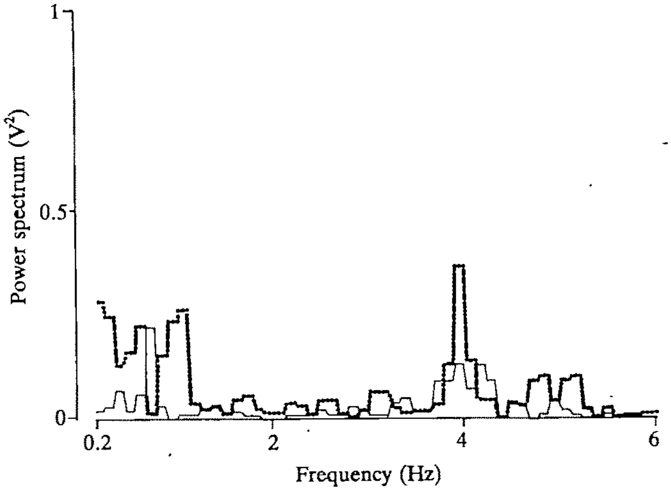

FIG. 6. Energy spectrum of the lateral sway in a patient with Parkinson's disease. Most of the activity occurs at frequencies below 1 Hz, apart from a peak of tremor at around 4 Hz. This was the only patient (*Case 4* in the Table) in whom the high frequency components of sway were of the same order of magnitude as the low frequency ones. Continuous line = eyes open; dotted line = eyes closed.

TABLE. LOW AND HIGH FREQUENCY COMPONENTS OF BODY SWAY IN 4 PARKINSONIAN PATIENTS.

			*2nd visual stimulus/1st visual stimulus**		
Case	*Tremor frequency*	*Tremor contribution to sway (%)*	*Sway path*	*Low frequency*	*High frequency*
1	6.4 Hz	0.004	0.65	0.45	0.11
2	6 Hz	0.01	0.56	0.07	0.2
3	6 Hz	0.17	0.74	0.30	1.39
4	4 Hz	24.68	0.94	0.95	0.87

* Ratio of body sway during the second room displacement/sway during the first room displacement. The data were obtained separately from sway path analysis and from measurements on the power spectrum at low (0.2–3 Hz) or high (tremor) frequencies.

Following reports that different cerebellar ataxias can be distinguished by specific sway patterns (Diener *et al.*, 1984) a comparison was made between the group of patients with diffuse ataxias and those with a cerebellar vermis syndrome in respect of visual control of sway. The 'Romberg quotient' for the diffuse ataxias was 2.19 SD ± 1.46 and for the vermis ataxias 1.88 ± 1.00; the visually-induced body sway (V.St−EO) was 5.22 ± 11.39 and 3.29 ± 3.21, respectively, and the ratio second/first visual stimuli 0.91 ± 0.30 and 0.67 ± 0.17. None of these values were significantly different between the groups. The values for the patient with a pure neocerebellar syndrome were 'Romberg quotient' 1.63, V.St−EO 0.56 and ratio second/first stimuli 0.43.

DISCUSSION

The presentation of a transient movement of the entire visual frame to a standing subject is a potentially destabilizing situation. If the subject assumes that the visual world is stationary and deduces that he himself is swaying, any postural adjustment made will be inappropriate for upright stance. The findings of the test are that on first presentation of the stimulus to normal subjects, their initial sway response is in the direction of room motion, presumably because the onset of room motion was interpreted as themselves swaying in the opposite direction. The secondary component of the sway response, which then brings the centre of gravity back to upright, and the subsequent attenuation of the response on repeated trials depend mainly on proprioceptive information from the lower limbs (Bronstein, 1986). Thus the visual stimulus of the moving room is a test of the relative strength of the visuopostural loop (which in this unusual situation is destabilizing) against that of the stabilizing vestibulo-proprioceptive-postural loops. In contrast, body sway with eyes open in a visually stable environment requires the synergistic action of the vestibuloproprioceptive and visual loops in balance control.

PD and CD patients showed distinct patterns of abnormal body sway compared with age-matched normal subjects. Cerebellar patients swayed more with eyes open, closed, and during visual stimulation and also had higher 'Romberg quotients' than normal controls. These findings indicate that although CD patients are more unsteady than normals in all situations they retain the ability to use vision to control much of their unsteadiness. Furthermore, on repeating the challenge of moving the room, they manage to suppress the destabilizing effect of visual stimuli showing that they have retained the ability to adapt their responses to this unusual stimulus. In support of this are earlier reports in CD patients whose spontaneous unsteadiness was made only slightly worse by optokinetic stimulation at constant angular speed in roll, but much worse on eye closure (Dichgans *et al.*, 1976). It would seem that the causes of unsteadiness in CD patients relate to basic disorders of muscle incoordination and regulation of vestibulo-proprioceptive reflexes (Holmes, 1956; Nashner and Grimm, 1978; Mauritz *et al.*, 1981), the visuopostural loop remaining largely unaffected by their disease.

Although Diener *et al.* (1984) reported that patients with vermal ataxias had a reduced ability to control their unsteadiness by vision, this was not a consistent feature in our cases with such diagnosis. Instead, a few patients with low 'Romberg quotients' were present in either group (diffuse or vermal) of ataxias; it is likely that this discrepancy can be explained by differences in the clinical criteria used to ascribe patients to one or another group. There are also reports attributing symptoms such as disorientation provoked by strong optokinetic stimuli to cerebellar disease (Hood, 1980) although such clinical material was not encountered in our own series.

The results in PD patients are in striking contrast in that, although all basic sway parameters were normal, the effect of room movement on their body sway was significantly greater than in normal controls and, more importantly, they had impaired ability to reduce body sway on a second presentation of the visual stimulus.

In normal circumstances, the relative weight of each sensory loop within the postural control system can be quickly modified. For instance, when the supporting surface is compliant or irregular the efficiency or gain of the visuopostural loop is increased (Talbott and Brookhart, 1980) and when the information relayed by the visual system becomes inappropriate or unreliable the relative weight of the visuopostural loop drops immediately (Bronstein, 1986). Our findings therefore suggest that the inability to reduce the unstabilizing effect of the visual stimulus found in PD patients represents the loss of this adaptive property by which the relative influence of each sensory loop on postural control is reweighted according to changes in the environment.

The enhanced responsiveness to room movement is consistent with more general evidence that PD patients tend to be selectively dependent on visual information for their motor activities (Martin, 1967; Flowers, 1976; Cooke *et al.*, 1978; Hood and Waniewski, 1984). The finding that the 'Romberg quotients' and the ratio second/first visual stimuli were positively correlated in the PD patients (*see* fig. 5) could be interpreted in terms of the loss of this adaptive property resulting from the patients' greater dependence on vision. However, the fact that CD patients were normally able to reweight the gain in the visual loop during room movement, in spite of being more unsteady and having higher 'Romberg quotients', indicates that a simple causal relationship between these two variables is unlikely. More probably, the increased dependence on vision and the loss of the adaptive reweighting mechanism for postural control are primary components of the PD syndrome. It may be that both defects co-relate to a third, more fundamental, abnormality in the visuomotor mechanisms.

A related question is whether the abnormal visual dependence in these patients is a primary component of the disease or whether it develops as a secondary phenomenon compensating for primary failures in other postural responses. Although we have not addressed this point directly, the experiments have shown that in the absence of adequate plasticity in the system the increased dependence on visual input is potentially destabilizing in these patients and therefore, by definition, does not always play a compensatory role. Of particular relevance is the demonstration by Teuber and Proctor (1964) that PD patients make large errors of overestimation in setting the visual or postural vertical following whole body tilt but are able to set the visual vertical correctly when positioned upright. These results indicate that an unusual vestibuloproprioceptive input produces, in these patients, an inability to make appropriate judgements in a visual task. Moreover, the kinds or errors made by PD patients were similar to those made by subjects with labyrinthine defects (Miller *et al.*, 1968), implying that vestibular/proprioceptive signalling is hypoactive in PD patients (Martin, 1965). Our experiments have shown that PD patients were made abnormally unstable when the room moved, although they had normal body sway when the room was stationary (eyes open or closed). This suggests that when sensory cues are congruent, PD patients can make use of vestibuloproprioceptive information but they seem unable to do so when visual input conflicts with other sensory cues. In these circumstances vision predominates. This, as with Teuber's findings, may reflect hypoactive vestibuloproprioceptive control but could also imply regression in motor control in these patients, since it has been shown that infants (Lee and Aronson, 1974) and lower species (Friedman, 1975; Gresty, 1975; Dieringer and Precht, 1982) are similarly 'hooked' on vision and have proportionally larger postural reactions to optokinetic stimuli.

The contribution of parkinsonian tremor to lateral sway was not significant. The point of note, however, is that patients with identifiable tremor on the power spectrum of the posturographic recordings were those with second/first visual stimulus ratios comparable to those in the normal controls. This observation agrees with previous clinical reports in large numbers of parkinsonian patients, showing a positive correlation between gait disorder and bradykinesia and an absence of correlation between disturbances of gait and presence of tremor (Lieberman *et al.*, 1980).

In summary, these studies have provided evidence that the cerebellum and the basal ganglia make distinct contributions to balance control. Despite general unsteadiness, the patients with cerebellar disease have relatively normal visual control of sway and rapidly learn to ignore misleading visual stimuli. In contrast, parkinsonian patients have enhanced responses to room movement and cannot adapt to repetition of the stimuli. The findings in PD patients show that they have a higher dependence on visual information for motor control and have a defect in the ability to deweight the visuopostural loop in favour of the vestibuloproprioceptive one. Since in the presence of congruent sensory cues PD patients had normal sway, these findings cannot be explained only in terms of an hypoactive proprioceptive-vestibular loop. It is suggested that the difficulty in adapting to a conflicting visual frame of reference represents a regression to a more primitive form of postural control.

ACKNOWLEDGEMENT

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EFFECTS OF BRAINSTEM LESIONS ON THE MASSETER INHIBITORY REFLEX

FUNCTIONAL MECHANISMS OF REFLEX PATHWAYS

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SUMMARY

The masseter inhibitory reflex (MIR) was investigated in 16 patients with localized brainstem lesions involving the trigeminal system. The MIR consists of two phases of EMG silence (S1 and S2) evoked by stimulation of the mental nerve during maximal clenching of the teeth. The extent of the lesions was assessed by neurological examination, nuclear magnetic resonance imaging (MRI), and recording of trigeminal reflexes with known paths (jaw jerk and blink reflex).

The MIR appeared to be abnormal in lesions involving the pontine tegmentum, from the pontomedullary junction to midpons, and some lesions selectively affected one component of the MIR, proving that S1 and S2 are relayed by independent circuits. The results indicate that afferent fibres for S1, which reach the pons via the trigeminal sensory root, enter the ipsilateral trigeminal spinal tract and terminate at the level of the midpons; impulses are then relayed by interneurons to the ipsilateral and contralateral trigeminal motor nuclei. The afferent fibres for S2 follow a similar path, but descend to the pontomedullary junction; at this level impulses are conducted along bilateral interneuronal paths, which probably ascend through the lateral reticular formation, before connecting with the trigeminal motor nucleus on either side.

Analysis of MIR recordings can be of particular value because brainstem inhibitory reflexes cannot be tested by clinical examination.

INTRODUCTION

Mechanical or electrical stimulation anywhere within the mouth or on the facial skin of the maxillary and mandibular trigeminal divisions evokes a reflex inhibition in the jaw-closing muscles. In man, these reflexes probably serve a protective function and are involved in the coordination of jaw movements during mastication and speech. The masseter inhibitory reflex (MIR), also called the cutaneous silent period or exteroceptive suppression, is evoked by electrical stimulation of the mental nerve and consists of early and late phases of electrical silence (S1 and S2), interrupting the voluntary electromyographic (EMG) activity in the ipsilateral and contralateral masseter muscles. The S1 response (10–15 ms latency) is mediated by medium-size myelinated afferents (Godaux and Desmedt, 1975; Cruccu *et al.*, 1987, 1989), and by an oligosynaptic circuit

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in the pons (Godaux and Desmedt, 1975; Ongerboer de Visser and Goor, 1976*a*; Cruccu *et al.*, 1984). The nature of the S2 response (40–50 ms latency) is controversial. It has been described as a proprioceptive silent period following a stretch reflex induced by S1, a nociceptive reflex, the second part of the single long-lasting silent period interrupted by a recurrence of voluntary activity, a pause due to the motoneurons being synchronized by S1, or a cutaneous reflex mediated by a multisynaptic circuit (Yemm, 1972; Yu *et al.*, 1973; Godaux and Desmedt, 1975; Ongerboer de Visser and Goor, 1976*a*; Cruccu *et al.*, 1984; Miles *et al.*, 1987).

The MIR can only be investigated by electrophysiological means and has been proposed as an aid for studying the chewing apparatus and pain sensation (Matthews, 1975; Sharav *et al.*, 1982; Lund *et al.*, 1983) as well as disorders of the trigeminal nerve, the brainstem and motor control from the cerebral hemispheres (Struppler *et al.*, 1963; Ongerboer de Visser and Goor, 1976*a*; Berardelli *et al.*, 1985; Cruccu *et al.*, 1987, 1988). Nevertheless, detailed data concerning central pathways of the MIR in man are not yet available.

In contrast to the MIR, much more is known in man about the pathways subserving the blink reflex (Kugelberg, 1952; Kimura and Lyon, 1972; Ongerboer de Visser and Kuypers, 1978) and the jaw jerk (McIntyre and Robinson, 1959; Ferguson, 1978; Ongerboer de Visser, 1982). These reflexes provide information on the trigeminal system at three different levels, extending from the most caudal brainstem area to the upper part of the midbrain. The blink reflex consists of an early brief response (R1) ipsilateral to the stimulated supraorbital nerve, and a late bilateral response (R2). The sensory trigeminal root is the common afferent limb; the facial nerve is the common efferent limb. R1 is relayed through an oligosynaptic arc in the pons. The afferent fibres for R2 descend from the pons through the spinal trigeminal tract in the lateral medullary region and terminate in the most caudal part of the spinal trigeminal nucleus. From this area R2 is conducted through ipsilateral and contralateral polysynaptic pathways, before making connections with the facial nuclei. These trigeminofacial connections probably run through the bulbar lateral reticular formation medial to the spinal trigeminal nucleus (Ongerboer de Visser and Kuypers, 1978). The jaw jerk circuit involves the ipsilateral midbrain and midpons; the afferents have their cell bodies in the trigeminal mesencephalic nucleus, which has collateral links with the trigeminal motor nucleus in the pons (McIntyre and Robinson, 1959; Darian-Smith, 1973; Ongerboer de Visser, 1982).

This study describes MIR changes in 16 patients affected by well-localized lesions of the brainstem, as assessed by clinical examination, nuclear magnetic resonance imaging (MRI), and recordings of the jaw jerk and blink reflex, to verify whether the two components of the MIR are relayed at different levels and to define the respective circuits.

METHODS

The patient group consisted of 16 patients, 7 females and 9 males, between the ages of 19 and 70 (mean 45) yrs. Clinical symptoms and MRI findings in the 16 patients, who were alert during the examinations, are summarized in the Table. In all patients, neurological examination was followed immediately by the reflex recordings.

Our method for studying the MIR has been reported previously (Ongerboer de Visser and Goor, 1976*a*; Cruccu and Bowsher, 1986; Cruccu *et al.*, 1987). EMG activity was recorded simultaneously from both masseter muscles by needle or surface electrodes (bandpass 20–5000 Hz). The mental nerve of either side was stimulated with single supramaximal electrical stimuli (0.1 ms duration) delivered by surface electrodes. The subject was instructed to maintain maximal clenching of the jaws for periods of about 3 s with the aid of audiovisual feedback. After every 10–30 s of rest, the contraction was repeated. At least 8 trials were repeated for each side of stimulation. One-sided stimulation evokes symmetric bilateral responses. The ipsilateral response is called 'direct', the contralateral response 'crossed'. Latency times of S1 and S2 were measured from the stimulus artefact to the start of S1 and S2, respectively. Normal values for latency and duration had previously been obtained in 35 healthy subjects between the ages of 24 and 78 (mean 49) yrs (Cruccu *et al.*, 1984, 1987). For S1 the upper limit of normal latency is 15 ms (mean + 3 SD) and the lower limit of normal duration is 9 ms (mean −3 SD). For S2 these values are 60 ms and 20 ms, respectively. A difference in latency time between the right and left side exceeding 2 ms for S1 and exceeding 5 ms for S2 is considered abnormal.

The blink reflex was evoked by electrical stimulation of the supraorbital nerve and recorded from the orbicularis oculi muscles, according to a technique described elsewhere (Ongerboer de Visser and Goor, 1974). The early R1 and late R2 are considered delayed if the latency exceeds 13 ms and 41 ms, respectively. A R/L difference in latency exceeding 1.5 ms for R1 and 8 ms for R2 is also considered abnormal.

The jaw jerk was evoked by tapping the chin with a triggered hammer. Details of the technique have been reported previously (Ongerboer de Visser and Goor, 1974, 1976*b*). A consistent unilateral absence, or a difference of more than 0.5 ms between the latencies on the two sides, are pathological findings.

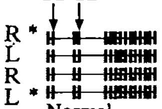
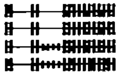
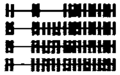
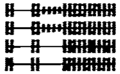
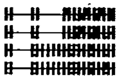
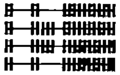
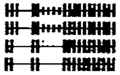
RESULTS

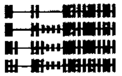
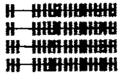
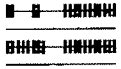
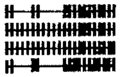
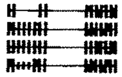
Descriptions of brainstem pathology and MRI location, clinical features and types of abnormal neurophysiological reflex and MIR findings are given in the Table. The 16 patients are presented according to the location of the lesion in the brainstem, in caudal-rostral and lateral-medial order. Abnormalities of the direct and crossed MIR to one-sided stimulation are attributed to lesions along the afferent paths, whether extrinsic or intrinsic, situated before the site of crossing of impulses, and are described as of 'afferent' type. Abnormalities of the direct and crossed MIR to one-sided stimulation plus abnormalities of the crossed MIR to contralateral stimulation are described as of 'mixed' type and are attributed to lesions at or after the site of crossing of impulses, as are abnormalities of the two crossed responses alone. None of the patients showed abnormalities confined to the muscle on one side, i.e., the 'efferent' type defect.

In 2 patients (A1, A2) who had a lesion in the lower medulla in the paramedian position, the MIR was normal bilaterally, indicating that the MIR circuits are rostral at this level.

In 2 patients (B1, B2) who had a lesion at the level of the pontomedullary junction, and in 3 (B3–5) with a lesion in the lower pons, the S2 component of the MIR was absent or abnormal, but S1 was normal, indicating that the circuits for S2 reach caudally to the pontomedullary junction and those for S1 are rostral to the lower pons (fig. 1). Cases B1, B3 and B4, with dorsolateral lesions, showed abnormalities of the direct and crossed S2 component to ipsilateral stimulation, that is, the 'afferent' type. Case B2 with a paramedian lesion showed 'afferent' type abnormalities plus absence of the crossed

TABLE. CLINICAL FINDINGS, BRAINSTEM LESIONS WITH THEIR LOCATIONS DEMONSTRATED BY NUCLEAR MAGNETIC RESONANCE IMAGING, AND ABNORMAL FINDINGS FROM RECORDED MASSETER INHIBITORY AND BLINK (FIRST AND SECOND RESPONSES, R1 AND R2, RESPECTIVELY) REFLEXES AND JAW JERK IN THE 16 PATIENTS WITH BRAINSTEM PATHOLOGY

Case sex, age (yrs)	*Pathology*	*MRI location*	*Clinical and reflex findings*	*MIR findings*	*MIR pattern* S1 S2
A1, M, 26	Tumour	Med. obl. C4, L paramedian	L trigeminal hypalgesia, L arm paresis. Bilateral abn R2 crossed responses	Normal	 Normal
A2, M, 19	Angioma	Med. obl., L paramedian	L trigeminal neuralgia, nystagmus, dysphonia, dysphagia, lateropulsion. Bilateral abn R2 crossed responses	Normal	Normal
B1, M, 70	Infarction	Pontomedullary junction, L dorsolateral	L trigeminal hypalgesia. L R2 'afferent' abn	L S2 'afferent' abn	
B2, F, 28	Infarction	Pontomedullary junction, L dorsomedial	L internuclear ophthalmoplegia	L S2 'mixed' abn	
B3, F, 67	Infarction	Lower pons, R dorsolateral	R trigeminal hypalgesia. R R2 'afferent' abn	R S2 'afferent' abn	
B4, M, 40	Tumour	Lower pons, R dorsolateral	L abducens and facial pareses. L R1 abn, L R2 'efferent' abn	L S2 'afferent' abn	
B5, M, 45	Arteriovenous malformation	Lower pons, midline	Opsoclonus, mild R facial paresis	Bilateral S2 crossed abn	
C1, M, 49	Demyelination	Midpons, R dorsolateral	R trigeminal neuralgia and hypalgesia. R R1 abn, R2 'mixed' abn	R S1 'afferent' abn, R S2 'afferent' abn	

C2, F, 41	Tumour	Mid+lower pons, L half	L trigeminal hypalgesia, L abducens and facial pareses, R hemiparesis. L R1 abn	L S1 'afferent' abn, L S2 'mixed' abn	
C3, F, 47	Haemorrhage	Mid+lower pons, midline	L > R abducens paresis, mild L facial paresis, vertigo, L hearing loss	L S1 'afferent' abn, bilateral S2 abn	
C4, F, 63	Tumour	Upper+midpons, L dorsolateral	L trigeminal hypalgesia, L trigeminal paralysis. L R1 abn, R2 'mixed' abn, L JJ absent	R S1 crossed abn, L masseter paralysis	
C5, M, 53	Haemorrhage	Upper+midpons, L paramedian	L abducens paresis, vertigo, R hemiparesis and hypalgesia. L R2 crossed abn	Bilateral S1 crossed abn, bilateral S2 crossed abn	
C6, F, 52	Inflammation	Upper+midpons, midline+ L paramedian	L trigeminal hypalgesia, R arm paresis. L R1 absent	L S1 'mixed' abn	
D1, M, 47	Arteriovenous malformation	Midbrain tegmentum, L half	L arm dysmetria. L JJ absent	Normal	Normal
D2, F, 52	Cyst (Listeria)	Midbrain tegmentum, L paramedian	R hemihypalgesia, ataxia and hypotonia. R JJ absent	Normal	Normal
D3, M, 24	Haemorrhage	Midbrain tegmentum, L paramedian	L ocular palsy, dilated pupil. L JJ absent	Normal	Normal

F = female, M = male, R = on right side, L = on left side, S1 and S2 = first and second phase of EMG silence, Med. ob1. = medulla oblongata. Abn = abnormal. MRI = magnetic resonances imaging. MIR = masseter inhibitory reflex. JJ = jaw jerk.

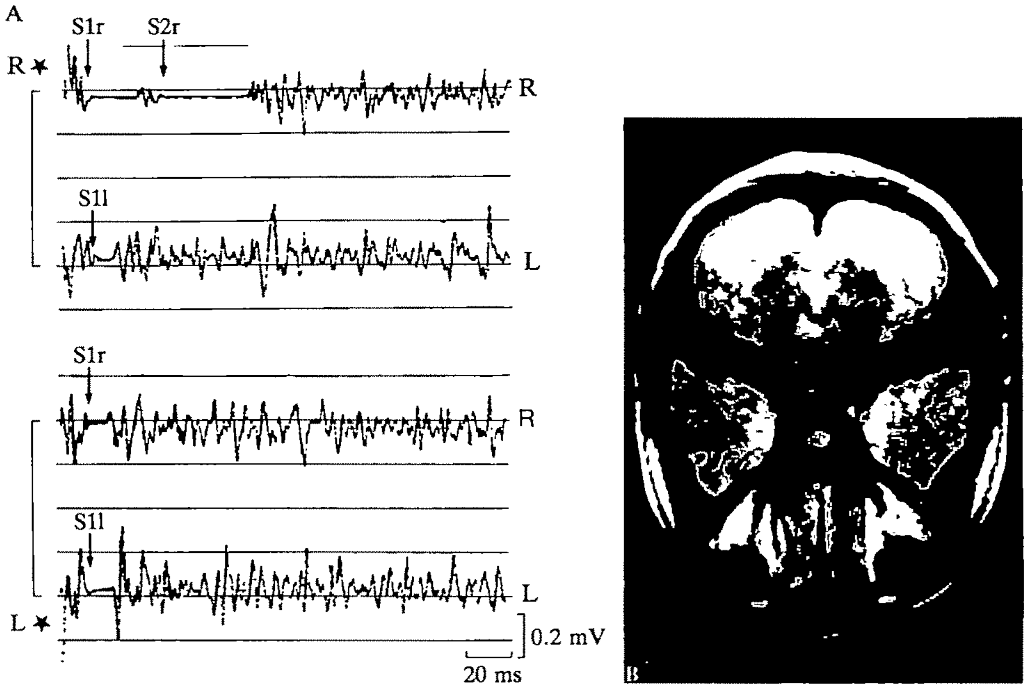


FIG. 1. A, 'mixed' type of abnormality of the masseter inhibitory reflex with simultaneous recordings from the right (R) and left (L) sides. In this patient (*B2*, *see* Table) the lesion is on the left. The *upper pair* of traces show normal first and second silent periods (inhibition) of EMG activity (S1 right (S1r) and S2 right (S2r), respectively) on the right (R), a normal S1 on the left (S1l), but an absent crossed S2l on the left (L) side (the side of the lesion) after stimulation of the right mental nerve (R*). The *lower pair* of traces show normal S1l and S1r but absent S2l and S2r silent periods (afferent block) after stimulation on the left mental nerve (L*). B, nuclear magnetic resonance imaging (MRI) scan (T_1 weighted) in *Case B2* (*see* Table) showing a small area of increased signal, probably an infarct, in the left dorsomedial half of the brainstem at the level of the pontomedullary junction. Abbreviations in A and B also apply to the subsequent figures.

S2 component to contralateral stimulation, that is, the 'mixed' type; Case B5, with a lesion at the midline, had a delay of the crossed S2 component to stimulation of either side (fig. 2); this indicates that the crossing of impulses for S2 is as caudal as the pontomedullary junction.

In 3 patients (C1–3) who had lesions in the midpons or extending from the midpons to the lower pons, and in 3 other patients (C4–6) with a lesion in the mid and upper pons, the S1 component was absent or abnormal, indicating that paths for S1 run through the midpons. Cases C2 and C3 had an 'afferent' defect of both the S1 and the S2 components and also abnormalities of the crossed S2 to contralateral stimulation, indicating that at the level of the mid and lower pons the paths for the crossed S2 are already contralateral, whereas those for the crossed S1 are not. In Case C5, with a paramedian lesion in the upper and midpons, the crossed S1 and S2 components to stimulation of either side were absent; Case C6, with two lesions in the upper and midpons, one on the midline and the other paramedian, showed a S1 'mixed' defect;

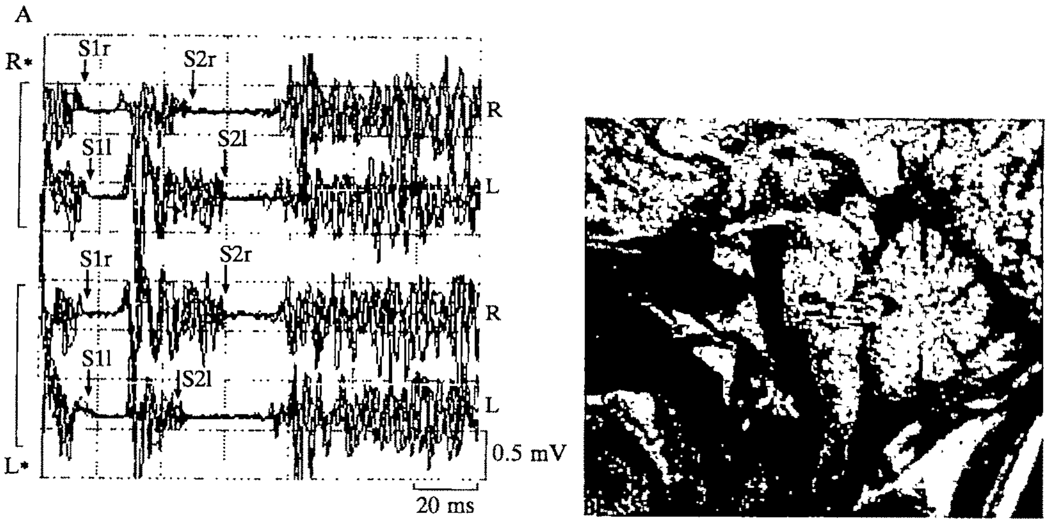


FIG. 2. A, delay of the crossed S2 component to stimulation of either side found in *Case B5* (*see* Table). The lesion is located in the lower pons just above the pontomedullary junction in the midline extending dorsally to the fourth ventricle. The *upper pair* of traces show normal S1r and S2r components on the right and a normal S1l with a delay of S2l on the left after stimulation of the right mental nerve (R*). The *lower pair* of traces show normal S1l and S2l components on the left and a normal S1r with a delay of S2r on the right after stimulation of the left mental nerve (L*). B, midsagittal MRI scan (T_1 weighted) in *Case B5* (*see* Table) showing an area of irregular intensity, probably an arteriovenous malformation, in the midline of the lower pons just rostral to the pontomedullary junction and extending into the fourth ventricle.

in Case C4, with a dorsolateral lesion in the upper and midpons, which involved the masticatory nucleus and made it impossible to study the MIR on the ipsilateral masseter, the crossed S1 component but not S2, was absent. Therefore only in lesions extending to the upper pons was the crossing of impulses for S1 impaired (C5, C6), and S2 spared (C4, C6).

In the 3 patients (D1–3) who had lesions in the midbrain tegmentum, the MIR was bilaterally normal, signifying that the MIR circuits are caudal to the midbrain.

DISCUSSION

The high rate of survival of most patients with small brainstem lesions means that the opportunity to correlate reflex abnormalities and autopsy findings arises only rarely (Masiyama *et al.*, 1985; Holtzman *et al.*, 1987). Computer tomographic x-ray scans are often insufficient to define or even identify small lesions at brainstem level. With the enhanced resolution of MRI, it is now possible to obtain more precise neuroanatomical relationships with neurophysiological findings. However, the functional and anatomical extent of the NMR 'lesions' are not necessarily coincident. We therefore also studied clinical symptoms and the blink and jaw reflexes, whose paths are already known in man, to obtain the best definition of the actual involvement of the trigeminal system.

The MIR was normal in patients with lesions located in the midbrain or at a lower medullary level. An earlier study, based on autopsy findings, gave similar results; the two components of the reflex, however, were not differentiated, and the paths were not defined (Ongerboer de Visser and Goor, 1976*a*).

The present study clearly shows that some lesions selectively affect one component, thus proving that S1 and S2 are relayed by independent circuits. This clarifies the nature of the S2 component and excludes the possibility that the MIR is a single long-lasting silent period interrupted by a recurrence of voluntary activity, or that S2 is merely a pause due to the motoneuronal synchronization induced by S1. Furthermore, since the patients with midbrain lesions and an absent jaw jerk had normal and symmetric S2 components, the possibility that S2 is a proprioceptive silent period following a stretch reflex induced by S1 is hardly tenable.

S2 was selectively affected in 5 patients, S1 in only 2. It could be argued that a larger summation at the interneuronal level could be required to evoke the long-latency S2, and the lesions involving the intrinsic route of the afferents would consequently affect S2 more severely than S1. This is highly improbable, since the threshold of stimulation for S2 is similar to that for S1—or even lower in some cases—and lesions of the afferents along their extrinsic route can selectively affect either S1 or S2, and more often S1 alone (Cruccu *et al.*, 1987), as happens with the R1 and R2 components of the blink reflex. In intrinsic lesions, selective S1 abnormalities are probably more unusual because the short S1 circuit lies in an area, the midpons, also reached by the rostral portion of the S2 paths.

On the basis of the present results and previous anatomical and electrophysiological data in human and animal experiments, the individual paths of S1 and S2 can now be drawn (fig. 3).

S1 circuit

The afferents for S1, belonging to the A beta fibre group (Goldberg and Nakamura, 1968; Kidokoro *et al.*, 1968*a*; Godaux and Desmedt, 1975; Nakamura, 1980; Cruccu *et al.*, 1987, 1989), reach the pons via the sensory root (Ongerboer de Visser and Goor, 1976*a*; Cruccu *et al.*, 1987).

In cats, the afferent impulses are not relayed by second order sensory neurons or excitatory interneurons, but directly reach an inhibitory interneuron probably located in the ipsilateral area 'h' which surrounds the trigeminal motor nucleus; the inhibitory interneuron projects onto ipsilateral and contralateral motoneurons (Kidokoro *et al.*, 1968*b*; Holstege and Kuypers, 1977; Holstege *et al.*, 1977; Nakamura, 1980). The crossing of impulses seems to occur at a level similar to that of the trigeminal motor nuclei, since medial pontine lesions at this level interrupt fibres crossing from area 'h' to the contralateral motoneurons (Holstege and Kuypers, 1977; Holstege *et al.*, 1977).

Also in man, S1 is mediated by an oligosynaptic circuit, given the lack of habituation to rhythmic stimulation, the rapid recovery cycle to paired stimuli, and the short latency gain to stimuli of increasing intensity (Godaux and Desmedt, 1975; Desmedt and Godaux, 1976; Cruccu *et al.*, 1984); the short central delay (Cruccu *et al.*, 1989) is compatible with two synapses. Anatomically, the afferent fibres probably run through the ipsilateral

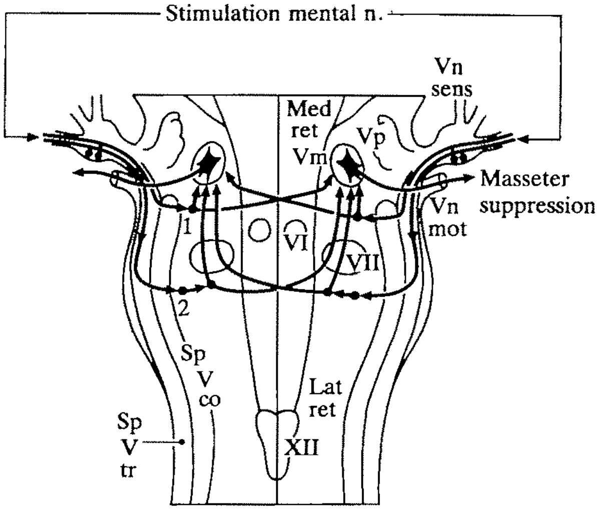


FIG. 3. Diagram showing the presumed location of interneurons subserving the two components of the masseter inhibitory reflex: (1) midpontine interneurons subserving the bilateral early component of EMG silence (S1); (2) interneurons, probably, located at the pontomedullary junction subserving the bilateral late component of EMG silence (S2). A lesion involving the spinal tract of the fifth cranial nerve (Sp V tr) with or without involvement of its nuclear complex (Sp V co) would only interfere with the bilateral S1 or S2 components, or both, elicited by stimulation of the mental nerve on the affected side. A larger lesion extending more medially or a paramedian lesion sparing the Sp V co would also interfere with S1 or S2, or both, ipsilateral to the affected side elicited by stimulation of the nerve on the intact side. Following a median lesion and depending on the extent of pathology, the lesion would interfere with S1 or S2, or both, contralateral to side of stimulation of the nerve on either side. Similar to the late blink and corneal reflexes the ascending routes are thought to be located in the lateral reticular formation (Lat ret). Vm = trigeminal motor nucleus. Vp = trigeminal principal sensory nucleus. VI = abducens nucleus. VII = facial nucleus. XII = hypoglossal nucleus. Vn mot = trigeminal motor nerve. Vn sens = trigeminal sensory nerve. Med ret = medial reticular formation.

spinal trigeminal complex, since 2 patients (C1, C2) with a dorsolateral lesion which involved the spinal trigeminal complex and produced a facial sensory loss had an 'afferent' S1 defect, that is, symmetric abnormalities of the direct and crossed S1 after ipsilateral stimulation. The circuit must be located at midpontine level, since we found S1 abnormalities only in lesions confined to or involving the midpons (C1 – 6). The crossing fibres, however, might extend rostrally to the upper pons (C5, C6).

S2 circuit

The afferents for S2 conduct at a similar velocity and are of similar fibre size to those for S1 (Godaux and Desmedt, 1975; Cruccu *et al.*, 1987), but are independent (Cruccu *et al.*, 1987); they reach the pons via the trigeminal sensory root (Ongerboer de Visser and Goor, 1976*a*; Cruccu *et al.*, 1987).

In cats, it has been observed that stimulation of the bulbar reticular formation at the pontomedullary junction exerts an inhibitory effect on the jaw-closing motoneurons of both sides, and that section of the brainstem below the trigeminal motor nuclei abolishes the late S2 component alone (Goldberg and Nakamura, 1968; Nakamura, 1980). The afferents probably project onto a chain of interneurons; the last interneuron lies in the medial propriobulbar system of the lateral reticular formation and gives ipsilateral and contralateral collaterals that ascend along the medial propriobulbar systems of both sides to reach the trigeminal motoneurons (Holstege and Kuypers, 1977; Holstege *et al.*, 1977; Nakamura, 1980).

In man, S2 shows a habituation rate, recovery cycle, and latency gain, compatible with a multisynaptic circuit (Godaux and Desmedt, 1975; Desmedt and Godaux, 1976; Cruccu *et al.*, 1984) unlike those of S1. Therefore, S2 impulses are relayed through a chain of interneurons before reaching the inhibitory interneuron.

In 2 of our patients (B1, B3) the occurrence of an S2 'afferent' defect with facial hypalgesia and a dorsolateral lesion involving the spinal trigeminal complex, suggests that S2 afferents enter the spinal trigeminal complex. In patients with lesions of the lower medulla (A1, A2) S2 was normal, but it was abnormal in patients with lesions as caudal as the pontomedullary junction (B1, B2). Abnormalities of the crossed response, that is, in the muscle on the same side as the lesion, were found in several patients with the most caudal lesions lying at the level of the pontomedullary junction or lower pons (B2, B5). This indicates that the crossing of impulses occurs in the caudal portion of the circuit. With respect to the lateral-medial distribution of fibre connections subserving S2, it would appear that ipsilateral and contralateral ascending paths lie close together and medial to the spinal trigeminal complex, in a paramedian position. Whereas dorsolateral lesions that involved the spinal trigeminal complex produced an 'afferent' defect, only lesions with involvement of the paramedian region produced 'mixed' type abnormalities (B2, C2). A large midline lesion can cause bilateral abnormalities of the direct and crossed responses (C3) by impairing the ascending paths bilaterally, while a small midline lesion shows abnormalities of the two crossed responses only (B5) by directly interrupting the crossing fibres.

All the lesions impairing the S2 ascending paths involved the lateral reticular formation (B2, C2, C3). It is probable that in man the interneurons for S2 also belong to the lateral reticular formation, as they do in the R2 component of the blink reflex (Ongerboer de Visser and Kuypers, 1978). That the S2 circuit is under the influence of corticoreticular projections onto the bulbar lateral reticular formation has already been suggested by findings in hemisphere lesions (Cruccu *et al.*, 1989).

Clinical significance

MIR recordings can be of particular value because brainstem inhibitory reflexes cannot be tested by purely clinical procedures. Abnormalities of the MIR were found in 5 patients with no clinical signs of impairment of the trigeminal system (B2, B4, B5, C3, C5), and in 3 of these, even other trigeminal reflexes (R1 blink reflex and jaw jerk) were all normal (B2, B5, C3). Finally, analysis of the S1 and S2 components helps in localizing the site of damage along the trigeminal paths. Extrinsic lesions rarely affect S2 alone, whereas intrinsic lesions rarely affect S1 alone. Bilateral abnormalities are frequent in intrinsic lesions and, if they affect the crossed responses only or are of the 'mixed' type, they undoubtedly are produced by an intrinsic lesion. The lesion involves the dorsal pontine tegmentum at the level of the midpons if both S1 and S2 are affected, and the lower pons or pontomedullary junction if S2 alone is affected.

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SYNAPSES, AXONAL AND DENDRITIC PATTERNS OF GABA-IMMUNOREACTIVE NEURONS IN HUMAN CEREBRAL CORTEX

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SUMMARY

Gamma-aminobutyric acid (GABA) containing neurons were characterized in human association cortex by a combination of Golgi impregnation and immunohistochemistry. Neurons were Golgi impregnated, gold toned, drawn and then classified on the basis of their dendritic and axonal arborization in layers I–VI. An antiserum to GABA was used to determine which of the impregnated neurons were immunopositive. Twenty-four GABA-positive cells were Golgi impregnated: 7 were bitufted with their dendrites predominantly radially orientated, and 17 were multipolar stellate cells. Three of the multipolar cells with large somata in the deep layers showed dendritic patterns similar to previously described basket cells. Nine of the multipolar stellate cells in layers III–VI showed characteristics of 'neurogliaform' neurons (Ramón y Cajal, 1899). The somata and the dendritic field of these cells were spherical, with diameters of about 10–15 μm and 200 μm, respectively. Their dendrites were smooth and slightly beaded. The axon collaterals were densely distributed in and around the dendritic field, in a spherical area with a diameter of at least 300 μm. The thin axon collaterals had only occasional 'en passant' swellings. Contacts between the axons of neurogliaform cells and the distal dendrites of Golgi-impregnated pyramidal cells were observed. Electron microscopic immunocytochemistry revealed that GABA immunopositive nerve terminals formed symmetric synaptic contacts with somata, with GABA immunonegative and immunopositive dendritic shafts and with dendritic spines. The results show that GABAergic neurons are heterogeneous with respect to their dendritic and axonal patterns. In addition to the chandelier and basket cells, which have been shown in animal studies to contain GABA, other cell types, most prominently the neurogliaform cells, terminating on the distal parts of neurons, also contain GABA and may have a inhibitory function. Many of the GABAergic terminals make synapses on dendritic spines and shafts in the human cerebral cortex.

INTRODUCTION

Golgi studies have demonstrated that the human neocortex, like that of other species, contains two major classes of neurons (Ramón y Cajal, 1899, 1909; Poljakov, 1953; Shkolnik-Jarros, 1962; Marin-Padilla, 1969; Braak and Braak, 1985). The first group consists of cells which possess numerous spines on their dendrites and includes the

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pyramidal cells and spiny stellate cells. Other cells have few or no spines on their dendrites. This latter category shows great variation in the shape and distribution of neuronal processes, with many varieties of neuron having been described on the basis of dendritic and axonal patterns (references as above). These aspiny neurons may have undergone differentiation during evolution, since smooth dendritic cells appear to form a more diverse population in primates than in lower species (Ramón y Cajal, 1899; Lund, 1987; Lund *et al.*, 1988).

There is evidence from subhuman species that many of the neurons with smooth or sparsely spiny dendrites contain gamma-aminobutyric acid (GABA) (Somogyi and Hodgson, 1985) or glutamate decarboxylase (GAD), the enzyme which synthesizes GABA (Ribak, 1978; Hendrickson *et al.*, 1981; Freund *et al.*, 1983). The organization of GABAergic neurons is of interest because GABA has been shown to be the major inhibitory transmitter in the cortex, and malfunction of the GABAergic system has been implicated in neurological disorders associated with the cortex (Lloyd *et al.*, 1984, 1985; Houser *et al.*, 1986; Ribak *et al.*, 1986; Chu *et al.*, 1987; *see also* Bernasconi *et al.*, 1984).

Very little is known about the neurochemical characteristics of any of the specific cell types in human cortex. The presence of GABA (Schiffmann *et al.*, 1988) and several neuroactive peptides (Dawbarn *et al.*, 1984; Chan-Palay *et al.*, 1985; Mai *et al.*, 1986; Chan-Palay, 1987; Sakamoto *et al.*, 1987) have recently been demonstrated in nonpyramidal cells, some of which probably belonged to the aspiny cell category. However, the processes of individual cells are rarely revealed by immunohistochemical staining in sufficient detail for the correlation of the immunohistochemically visualized cells with those revealed previously with single cell staining methods. Therefore, for the characterization of neurons both in terms of their molecular composition and the distribution of their processes we have combined Golgi impregnation and immunocytochemistry of the same cells (Freund *et al.*, 1983; Somogyi *et al.*, 1985; Kisvárday *et al.*, 1986*b*). Immunocytochemistry for GAD or GABA reveals the chemical nature of the cells, while the Golgi deposit demonstrates the processes, and provides a basis for the interpretation of the neuron's place in the network.

This strategy has been applied here for the characterization of GABA-containing neurons. In particular we were interested to see if different types of GABAergic neurons could be identified on the basis of the distribution of their processes. The results show that in addition to cortical neurons such as chandelier cells (Somogyi *et al.*, 1985) and basket cells (Somogyi and Soltész, 1986; Kisvárday *et al.*, 1987) which have been shown in animal studies to contain GABA, other cell types, with different axonal and dendritic patterns, also contain GABA.

EXPERIMENTAL PROCEDURES

Materials used in the present study were taken from biopsies of 4 patients with their informed consent. Two of them had temporal lobe epilepsy and had undergone temporal lobectomy. The superior temporal gyrus was examined. They were P.W., a 15-yr-old male and S.G., an elderly female of unknown age.

One female patient M.E.C., 73-yr-old, had an olfactory grove meningioma and part of her anterior orbital gyrus was removed. The fourth patient, A.M., a 45-yr-old male, had a deep glioblastoma and his posterior orbital gyrus was removed. There is no reason to assume that the cortical tissue examined from the 2 tumour cases was abnormal. In the temporal lobe patients the tissue showed no obvious sign of abnormality with any of the methods examined in the present study. All cell types were seen in all the areas examined, therefore the results will be described together.

Tissue processing

Cortical tissue blocks of about 4×4×6 mm were removed and washed free of blood in ice-cold oxygenated Tyrode solution for a few minutes. They were transferred to a fixative containing glutaraldehyde (1.25 or 2.5%, TAAB Laboratories), paraformaldehyde (1 or 4%, TAAB) and approximately 0.2% picric acid, all made up in 0.1 M sodium phosphate buffer (PB), at pH 7.4. After 5–10 min the blocks were cut into thinner slices in order to enhance the penetration of the fixative. Immersion fixation continued for 7–15 h. After this the slices were extensively washed in 0.1 M phosphate buffer and processed for rapid Golgi impregnation as described earlier (Somogyi *et al.*, 1981). Briefly, the blocks were treated with osmium tetroxide (0.5% in PB) for 2–6 h, and placed in 3.5% $K_2Cr_2O_7$ for 1–2 days. Alternatively they were placed in a solution containing 0.5% OsO_4 and 3.5% $K_2Cr_2O_7$. Thereafter the blocks were immersed in 0.5–0.65% $AgNO_3$ overnight, followed by sectioning on a Sorvall TC-2 tissue chopper at 70–80 μm. Areas containing Golgi-impregnated cells were illuminated for 10–30 min under an illuminator device, followed by processing for gold toning (Fairén *et al.*, 1977) with modifications (Somogyi *et al.*, 1981). The sections were dehydrated and then mounted on slides in resin (Durcupan ACM, Fluka). Golgi impregnated and gold toned neurons were then selected, drawn with the help of a drawing tube using ×100 oil immersion objective. Most neurons were reconstructed from only one or two sections, therefore their processes cut at the surface of the sections are not represented. In some cases, however, dendrites were followed over 4–5 sections comprising about 300–350 μm thick slab of tissue. The selected neurons were also photographed in a light microscope.

Postembedding GABA immunocytochemistry on semithin sections of Golgi impregnated neurons

Small areas containing the selected neurons were reembedded in resin, and 0.5 or 1.0 μm semithin sections were cut from the cell bodies. The sections were mounted on chrome-alum gelatine-coated slides and processed for postembedding GABA immunostaining (GABA serum code No. 9; Hodgson *et al.*, 1985) following a previously reported unlabelled antibody peroxidase-antiperoxidase procedure (Somogyi and Hodgson, 1985). The gold/silver precipitate marking the Golgi-impregnated cell appears as a thin rim of grey deposit along the somatic plasma membrane. The immunoreaction end product produced by peroxidase from the chromogen 3,3′-diaminobenzidine appears as a brown deposit over the entire cell including the nucleus. The two precipitates are therefore easily distinguished on the basis of both colour and location.

To assess method specificity some sections were incubated with antiserum to GABA that was preincubated with GABA conjugated to polyacrylamide beads (Hodgson *et al.*, 1985).

Postembedding GABA immunocytochemistry on electron microscopic sections

The fine structural preservation of the Golgi material was not suitable for electron microscopic examination. In order to study the postsynaptic elements of GABAergic nerve terminals GABA immunoreactivity was studied in ultrathin sections of the temporal cortex by an immunogold method (Somogyi and Soltész, 1986). Blocks fixed in a fixative containing 2.5% glutaraldehyde and 0.5% paraformaldehyde in 0.1 M PB at pH 7.4, were treated with OsO_4 and embedded in epoxy resin (Durcupan ACM, Fluka). Ultrathin sections were mounted on single slot formvar coated gold grids, and immunoreacted for GABA, using IgG coated 15 nm colloidal gold (Janssen Life Sciences) as the final marker. Immunopositive cells and terminals appear densely covered with gold particles.

To assess method specificity some grids were incubated with antiserum to GABA that was preincubated with GABA conjugated to polyacrylamide beads (Hodgson *et al.*, 1985).

Layering of the cortex

Specimens for this study were taken from different areas of the human cortex. Laminar boundaries of each cortical area were determined in 1 μm thick sections counterstained with a mixture of toluidine blue and Azur II. The layering of the cortex (fig. 1) was adopted from the work of Von Economo (1927). The layers of different cortical areas have different thickness. The location of each Golgi-impregnated cell was determined in relation to the nearest laminar boundary, and the cell was placed in the composite drawings according to its relative position to that boundary (figs 2, 3).

RESULTS

Controls

There were no immunopositive neurons or dots in sections which were reacted with antiserum preincubated with solid phase conjugated GABA. In the immunogold series only a few scattered gold particles were observed in control sections, and there was no accumulation of gold over any cellular profile.

GABA immunoreactivity in cortex

Using the peroxidase-antiperoxidase method and 3,3′-diaminobenzidine as chromogen, the immunopositive cells were dark brown. All layers contained immunopositive neuronal somata as assessed in semithin sections (fig. 1). Layers II and upper III appeared to contain a higher density and smaller GABA-positive somata than the other layers (fig. 1). The white matter also contained a few elongated GABA-positive neurons. In addition to the labelling of neuronal cell bodies, the neuropil contained immunopositive fibres and puncta (figs 4, 6). Many of the latter corresponded to nerve terminals and were often seen to surround immunopositive and immunonegative cell bodies (fig. 6F, H). In some of the samples many glial cells showed weak immunoreactivity; in others glial cells were negative for GABA.

Not all sections could be used; those from the middle of the blocks showed no immunoreactivity, and other sections showed uneven immunoreactivity due to the uneven penetration of the fixative into the tissue blocks.

GABA immunostaining of Golgi impregnated cells

The processes of GABA-positive cells were studied by Golgi impregnation. For technical reasons Golgi impregnation was performed first, therefore the processes of cells were drawn and photographed before the immunoreaction in order to keep a record of neurons before they were resectioned for immunocytochemistry. Altogether 51 nonpyramidal neurons were tested for the presence of GABA. An additional 70–80 Golgi-impregnated pyramidal cells had their cell bodies in the same sections and were thus also present in the immunoreacted sections.

None of the Golgi-impregnated pyramidal cells were immunopositive (fig. 4A, B), and other unimpregnated pyramidal cells were also immunonegative. In contrast 24 (N_1-N_{24}) of the Golgi-impregnated nonpyramidal cells were immunopositive for GABA (figs 2, 3, 4, 6).

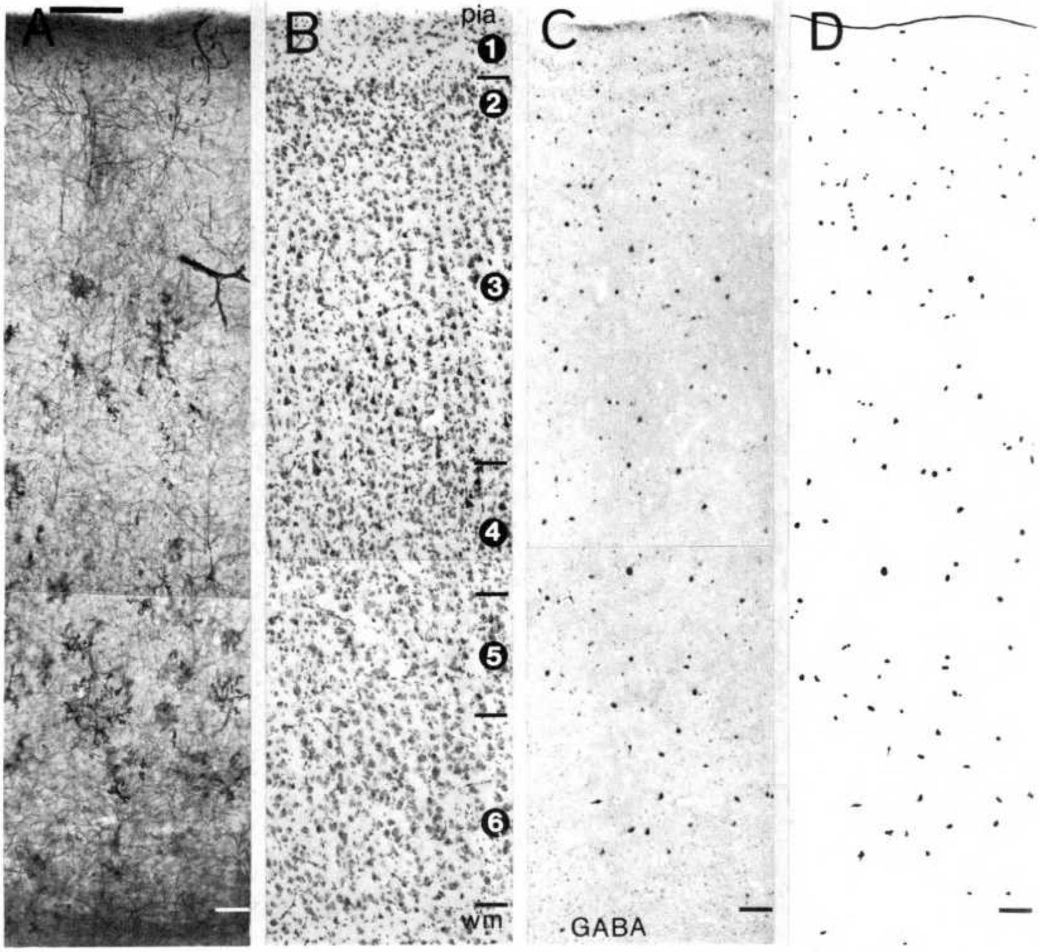

FIG. 1. Distribution of GABA-positive cells in the temporal cortex. A, light micrograph of a 70 μm Golgi impregnated, gold-toned section similar to those used for analysing impregnated cells. B, Nissl stained section from the same area used for delineation of laminar boundaries. C, GABA-immunoreacted 0.5 μm section cut from a Golgi impregnated section similar to that shown in A. D, drawing of the same section shown in C. Each dot represents a GABA-positive neuronal cell body. Note the differences in the size and density of GABAergic cell bodies in different laminae. Bar, top left (A−C) = 200 μm; wm = white matter.

Any particular neuron can be immunonegative either because it does not synthesize GABA in detectable amounts, or because its GABA content was not preserved by our procedure. The lack of staining in itself cannot be used as evidence for the absence of GABA in vivo in the immunonegative cells. In the following, therefore, only the immunopositive neurons will be described.

On the basis of dendritic arborizations two broad categories of GABA-positive cells can be recognized. One group, known from previous Golgi studies as 'bitufted cells', has predominantly radially orientated dendrites (i.e., direction of pia to white matter), often confined to a narrow column. The other group has a 'multipolar' dendritic field. Within both groups, but particularly in the latter, there are differences in soma and dendritic field size, in the number of dendrites and in axonal patterns. For some neurons only the soma and the dendrites were revealed ($N_{1,2,6,10,12,14,15}$ in fig. 2); the axons were probably not impregnated because of their myelin sheaths. While recognizing that only the characteristics of both axonal and dendritic patterns together allow the unequivocal identification of neuronal categories, for the purpose of presentation GABA-positive cells with common features are described together below.

Bitufted cells ($N_{3,5-11}$, *fig. 2*). They were all in layers II–IV. Obviously heterogeneous in some size (9–15 μm), they had the common feature of a predominantly radially oriented, elongated dendritic field. The somata were usually also radially elongated. The axonal branches, when they could be followed, also showed a predominantly radial course ($N_{5,7,9}$). An axon could originate from either the upper or the lower pole of the soma (N_9 and N_3, respectively), although some cells emitted axons from a major proximal dendritic shaft ($N_{5,11}$). Dendrites of several cells had thorny protrusions or appendages (e.g., neurons $N_{8,11}$), while other neurons exhibited beaded or smooth dendritic processes (e.g., $N_{6,9,10}$).

Large multipolar cells ($N_{12,14,15}$, *fig. 2*). Three neurons had somata of 18–24 μm diameter and few long dendrites, running up to 500 μm from the soma. The dendrites were beaded and smooth, only 1 cell (N_{15}) having occasional protrusions. The axons were not impregnated beyond the axon initial segment and in 2 instances ($N_{14,15}$) a thick myelin sheath could be recognized at the point when impregnation ceased.

Neurogliaform cells (N_{16-24}, *figs 3, 5, 6*). Their name derives from Ramón y Cajal (1899), and reflects the dense dendritic and axonal fields. These were the most frequently encountered nonpyramidal neurons in this material. Sixteen Golgi-impregnated neurogliaform cells were identified in the present material, 9 of which (N_{16-24}, fig. 3) were tested for the presence of GABA, and were found to be GABA-positive (fig. 6). These cells were found in layers III–VI, and their dendritic and axonal fields did not seem to respect laminar boundaries.

The somata were mostly spherical and relatively small, 10–15 μm in diameter (figs 3, 6). The main dendrites radiate from all parts of the soma and the primary dendrites tended to branch close to their origin. The dendritic fields were dense and spherical with a diameter of about 200–250 μm. Occasionally individual dendrites terminated as far as 300 μm ($N_{17,20,24}$, fig. 3). The dendrites were invariably smooth and lightly beaded (fig. 5).

The axons of neurogliaform cells originated either from the soma or one of the main dendritic trunks (fig. 3). The main axons emitted collaterals dichotomously and the branches did not differ markedly from subsequent branches. The fine collaterals intermingled with the dendritic tree (fig. 5). The axonal fields were generally spherical and exceeded the dendritic fields, spreading to a size of up to 300–400 μm in diameter. Individual axonal collaterals extended up to 500 μm, suggesting that the axonal field could be larger than traced in our sections. A characteristic feature of the thin axon collaterals was their wavy, frequently changing course, interrupted by occasional straight

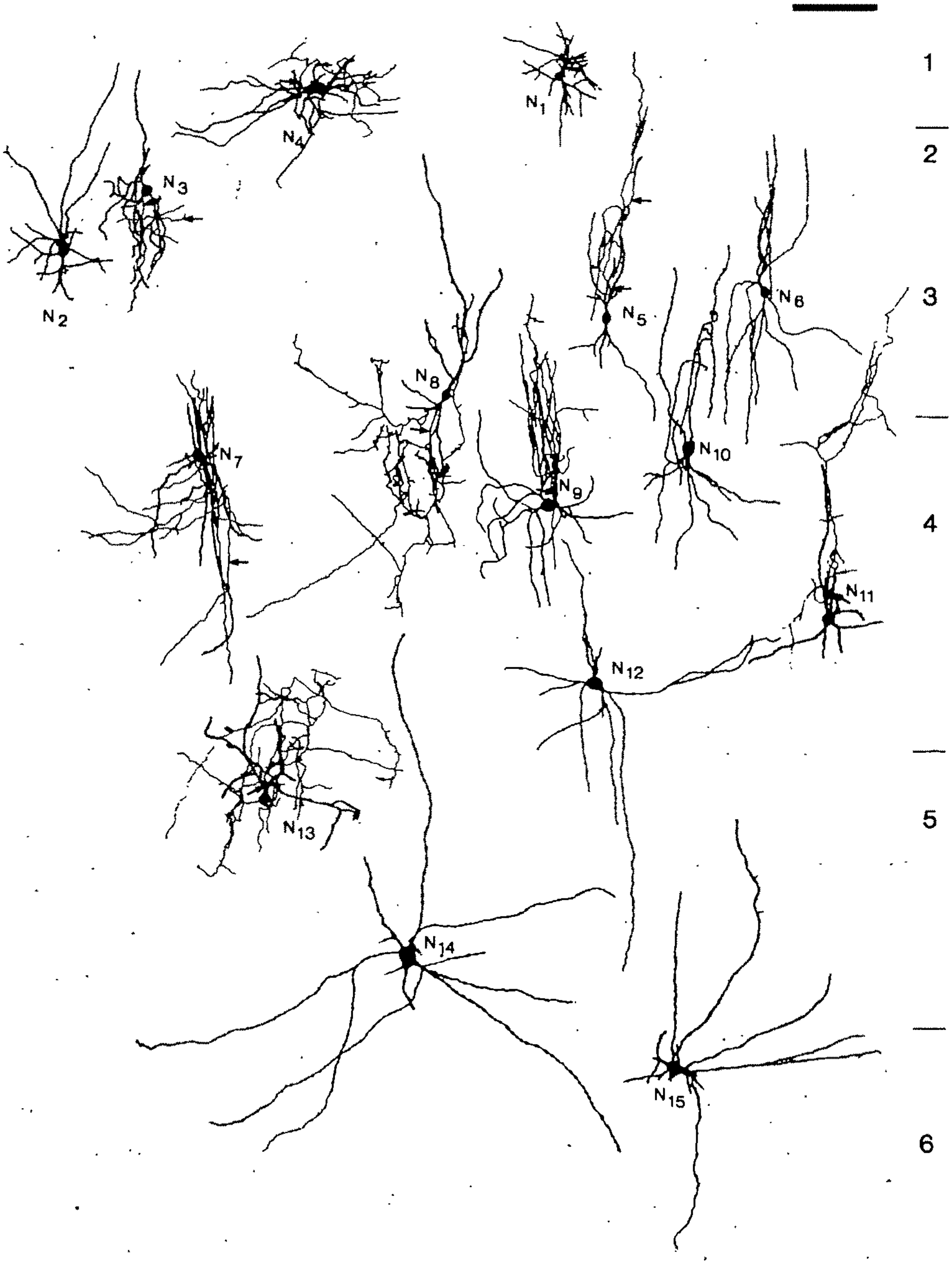

FIG. 2. Drawings of GABA-immunoreactive neurons. Dendritic and axonal arbors were revealed by Golgi impregnation. Only the dendrites and somata were impregnated of neurons $N_{1,2,6,10,12,14,15}$. For neurons $N_{3-5,7-9,11,13}$ axons (arrows) were also revealed. Note the differences in somatic size, axonal and dendritic patterns. Bar = 100 μm.

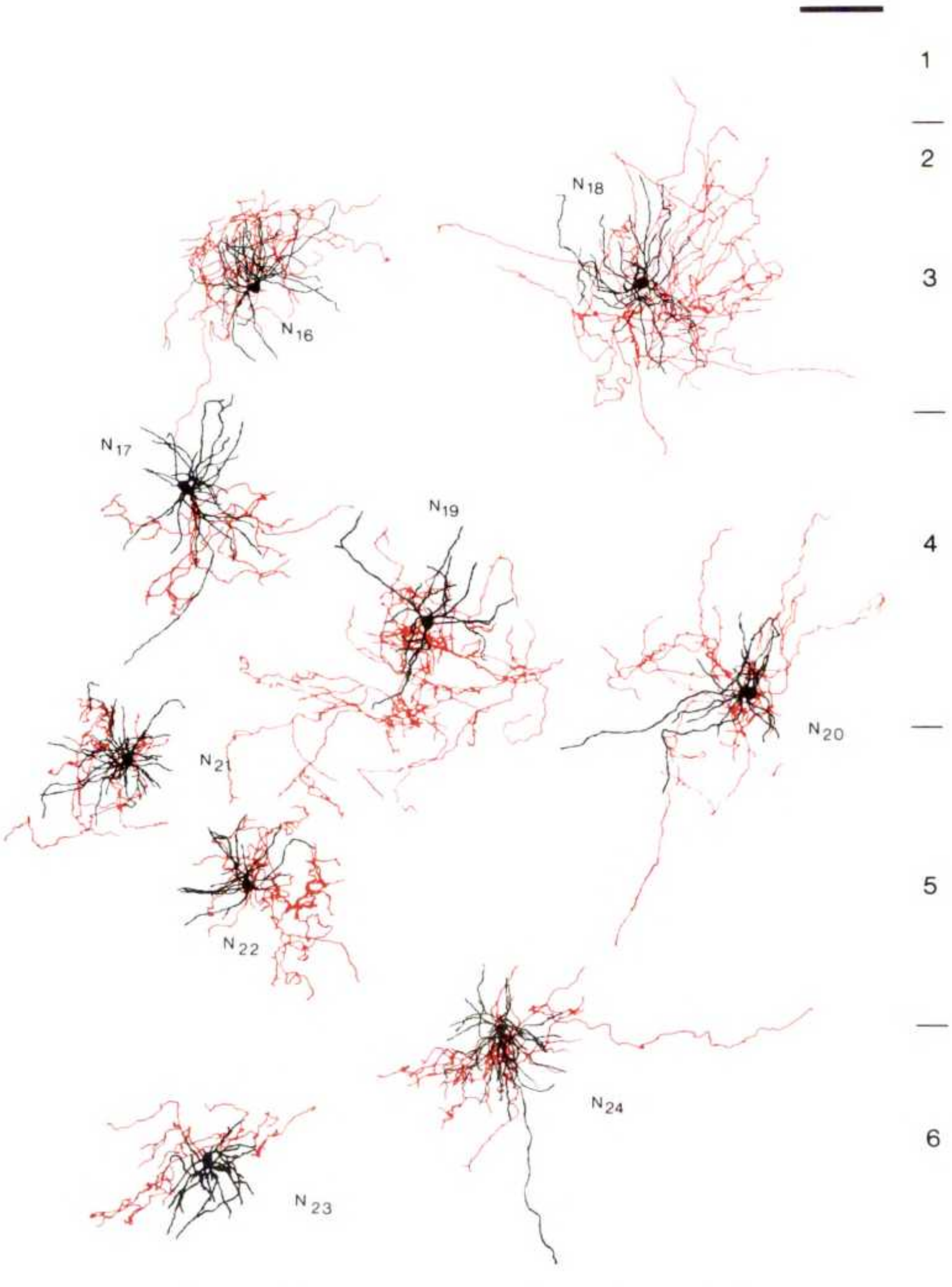

FIG. 3. Drawings of GABA-positive neurogliaform neurons, demonstrating their axonal (red) and dendritic (black) arbors by Golgi impregnation (N_{16-24}). Bar = 100 μm.

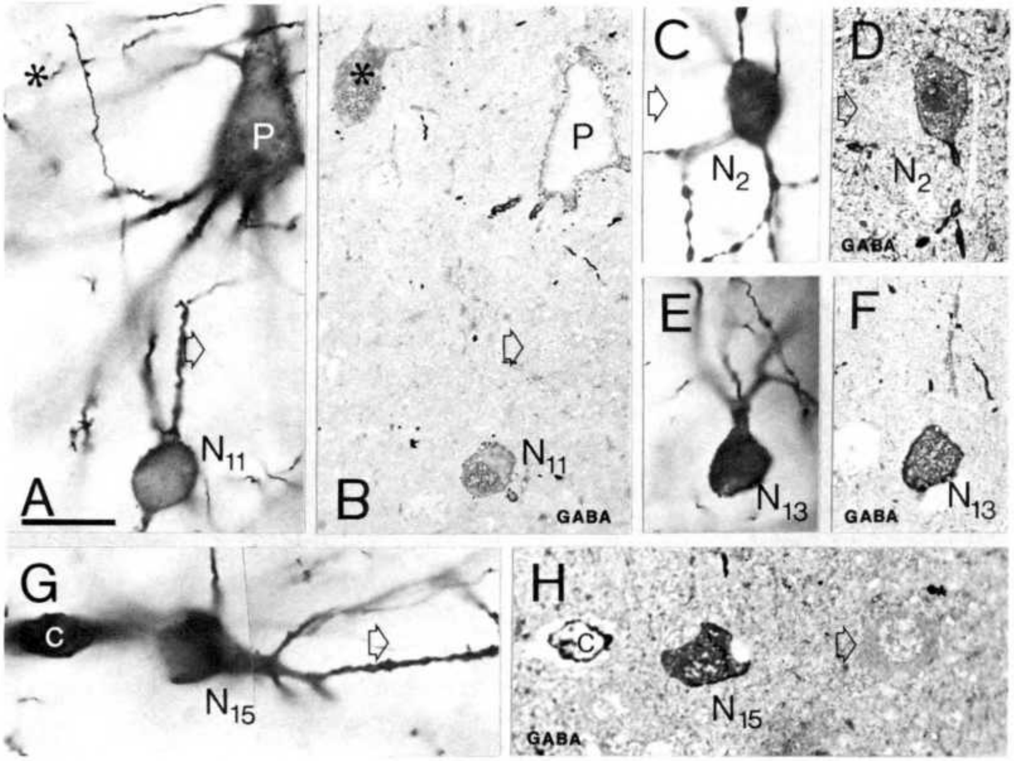

FIG. 4. Demonstration of GABA immunoreactivity in Golgi-impregnated cells. A, C, E and G are light micrographs of cells N_{11}, N_2, N_{13} and N_{15} (drawings are shown in fig. 2) taken from the 80 μm gold-toned sections. B, D, F and H are 0.5 μm sections of the same cells processed for postembedding GABA immunostaining. The peroxidase reaction end product in the somata shows that these impregnated cells are GABA-positive. Other immunopositive (asterisks) and immunonegative somata (arrows) are also visible. A Golgi-impregnated pyramidal cell (P) is GABA-immunonegative, as demonstrated in A and B by the lack of reaction end product within the thin marginal gold deposit (B). A blood vessel (C) impregnated in G and H is marked. Bar (A – H, same magnification) = 20 μm.

stretches. The axons formed exclusively 'en passant' varicosities, which were infrequent and small, hardly thicker than the axon collaterals (fig. 5). The axonal branches of the Golgi impregnated neurogliaform cells were seen to be in direct contact with distal dendrites of Golgi-impregnated pyramids, but never with the somata of other neurons.

Other GABA-positive neurons ($N_{1,2,4,13}$, *fig. 2*). These cells, while resembling previously reported neurons in primates, were not similar to those described above. They probably represent individual examples of cell types rarely found in our material. Two neurons were in layer I with contrasting features. One (N_1) was the smallest multipolar GABA-positive cell with 8 μm soma diameter and a dendritic field largely restricted to layer I. The other neuron (N_4) in layer I had larger somata and a horizontally orientated dendritic arborization, with an axon that also branches in layer I. Only the dendrites of a neuron in layer II (N_2) were impregnated. This neuron was not included into the bitufted category because its dendrites spread in a radial manner from

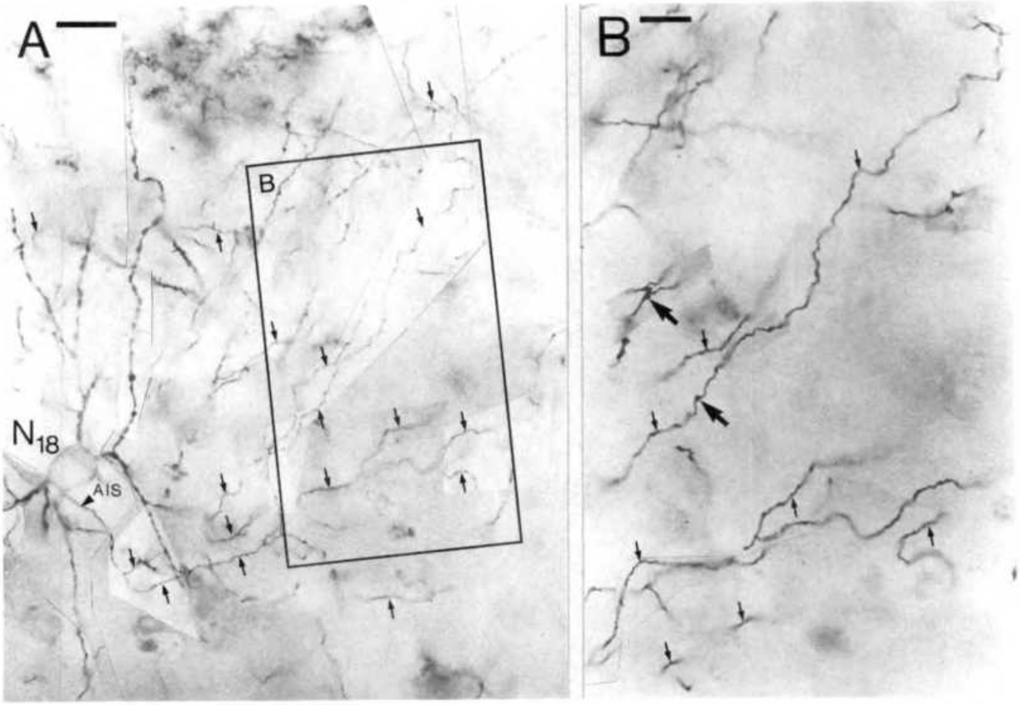

FIG. 5. Light micrographs of a Golgi-impregnated neurogliaform cell (N_{18}, *see also* fig. 3) in layers II/III. Note the thin undulating axon collaterals (small arrows) with sparsely distributed varicosities (large arrows). Bars = 20 μm.

the cell body. One neuron (N_{13}, fig. 2) at the border of layers IV/V somewhat resembled the neurogliaform cells described above, but it had relatively few dendrites and these were densely covered with thorns and spine-like protrusions. The axon of this labelled neuron also had boutons on short stalks.

GABA immunostaining of synaptic terminals. The poor fine structural preservation of the impregnated material did not allow direct studies on the synaptic connections of the Golgi labelled GABA-positive cells. Because the axons of bitufted and neurogliaform cells did not seem to contact the somata of other cortical neurons it is possible that these cells only contacted dendrites or spines in the neuropil. To examine this possibility the distribution of synapses established by GABA-positive boutons was studied in electron microscope sections.

GABA-positive terminals were found in all layers and they established type II (Gray, 1959), or symmetric synapses (fig. 7). The postsynaptic targets of GABA immunoreactive terminals were identified on the basis of ultrastructural features in serial sections. Dendritic shafts were identified on the basis of the presence of mitochondria and ribosomes. Dendritic spines lacked mitochondria and a spine apparatus was often observed. The postsynaptic elements were neuronal soma, dendritic shafts, dendritic spines and rarely axon initial segments. Both major thick dendrites with 1–2 μm diameter and small

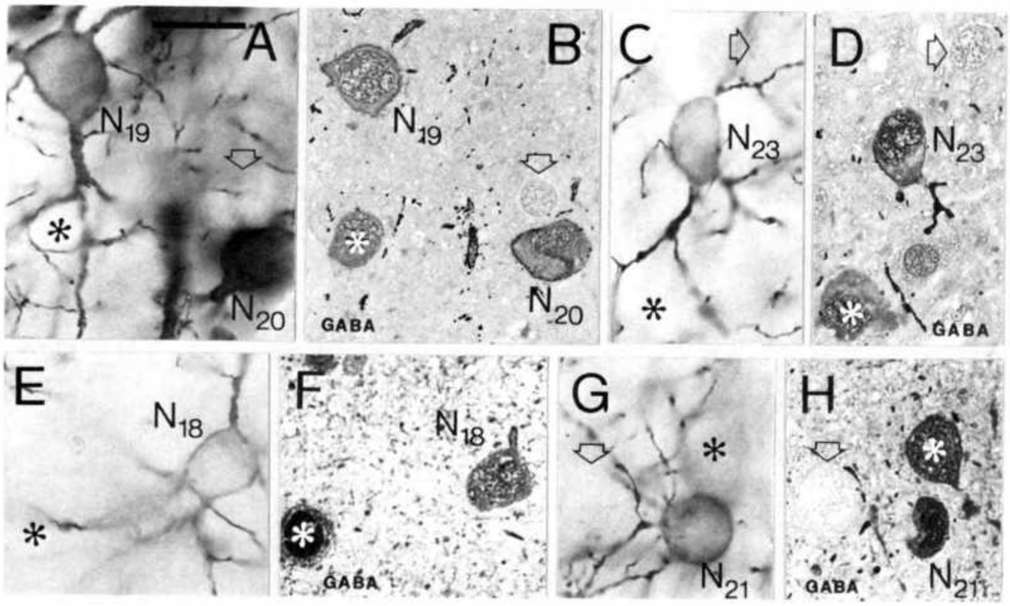

FIG. 6. Demonstration of GABA immunoreactivity in Golgi-impregnated neurogliaform cells. A, C, E and G are light micrographs of cells N_{19}, N_{20}, N_{23}, N_{18} and N_{21} in gold-toned thick sections (*see* drawings in fig. 3). B, D, F and H show the same cells in 0.5 μm semithin sections following the postembedding GABA immunostaining. Unidentified GABA-positive neurons (asterisks) and some of the nonimmunoreactive neurons (arrows) are also indicated. Bar (A–H) = 20 μm.

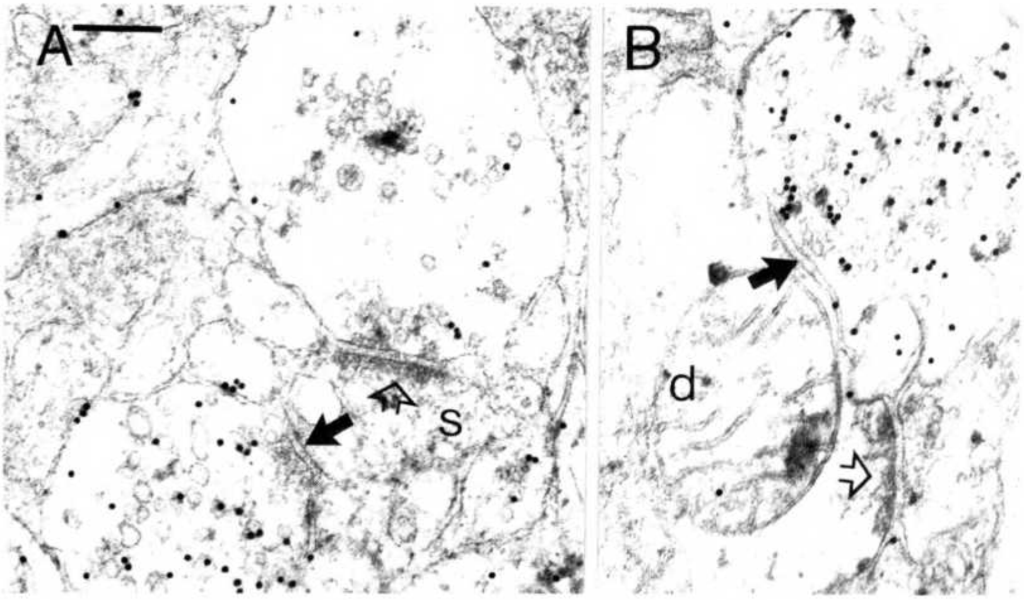

FIG. 7. Electron microscopic immunogold demonstration of GABA in synaptic boutons in human temporal cortex. A dendritic spine (s) in A, and the dendritic shaft (d) in B receive synapses (solid arrows) from GABA-immunopositive terminals, as shown by the selective accumulation of gold particles. The GABA-positive terminals established type II (solid arrow), the GABA negative terminals establish type I synapses (open arrow), with the same postsynaptic structures. Bar (A, B) = 0.2 μm.

dendrites with less than 1 μm diameter were seen to receive GABAergic synapses (fig. 7A, B). In addition to the GABA terminals on dendritic shafts and spines, the same postsynaptic structures frequently received type I synapses from unlabelled terminals (fig. 7).

DISCUSSION

Characteristics of cortical GABAergic neurons

In all cortical areas GABA is a major inhibitory transmitter (Krnjević and Schwartz, 1967; for reviews, *see* Krnjević, 1984; Alger, 1985). As demonstrated in subhuman species most of the GABAergic neurons that contribute to cortical GABAergic innervation are localized within the cortex, and comprise between 15 and 25% of cortical neurons (Ribak, 1978; Hendrickson *et al.*, 1981; Gabbott and Somogyi, 1986; Fitzpatrick *et al.*, 1987; Hendry *et al.*, 1987). Studies using radiolabelled GABA uptake (Hökfelt and Ljungdahl, 1972; Chronwall and Wolff, 1980; Hendry and Jones, 1981; Somogyi *et al.*, 1981), immunohistochemistry with antibodies to glutamate decarboxylase (GAD), the enzyme that synthesizes GABA (for review, *see* Houser *et al.*, 1984), or using antibodies to GABA itself (for review, *see* Ottersen and Storm-Mathisen, 1984) showed that both in primates and in subprimate species all GABAergic neurons are nonpyramidal cells. Nonpyramidal neurons have been described in great detail using Golgi inpregnation in the cortex of man (Ramón y Cajal, 1899, 1909; Poljakov, 1953; Shkolnik-Jarros, 1962; Seldon, 1981; Meyer, 1987), and animals (*see* e.g., Valverde, 1971; Lund, 1973; Szentágothai, 1973; Jones, 1975; Feldman and Peters, 1978; Peters and Regidor, 1981; Meyer, 1983). It has been demonstrated that they comprise a heterogeneous population in terms of their synaptic connections (Somogyi, 1977; Peters and Fairén, 1978; Peters and Proskauer, 1980; Peters and Kimerer, 1981; Somogyi and Cowey, 1981; Kisvárday *et al.*, 1985, 1986*a, b*; DeFelipe and Fairén, 1988), and therefore also in their position in the cortical network. It has also been shown in subhuman species that GABAergic interneurons are heterogeneous not only morphologically but also in their content of neuroactive peptides (Hendry *et al.*, 1984; Somogyi *et al.*, 1984) and cell surface molecules (for review, *see* Naegele *et al.*, 1988). Some human nonpyramidal cells share glycosyl groups with GABAergic cells in other species (Nakagawa *et al.*, 1986*a, b*).

It has been difficult to correlate the neurons revealed in immunocytochemical studies with particular classes of neurons demonstrated by intracellular cell filling or impregnation. While immunostaining showed that there was a great variation in the size and shape of GAD and GABA immunopositive neuronal somata, their dendritic and axonal patterns were poorly revealed. Subsequently, using immunocytochemistry with antibodies to GABA in combination with other methods, it could be shown that the GABA-containing neurons are of distinct categories (Somogyi and Hodgson, 1985; Somogyi and Soltész, 1986). In these studies, using Golgi impregnation or intracellular injection of horseradish peroxidase to visualize the processes of cells, it was shown that different classes of GABAergic neurons differ in their synaptic target selectivity. One variety of GABA- (Somogyi *et al.*, 1985) and GAD-containing cell (Freund *et al.*, 1983), the so-called chandelier or axo-axonic cell, establishes synapses exclusively with the axon initial segments of pyramidal cells. In contrast two other classes of cells the large basket cells and clutch cells terminate on the somata, dendritic shafts and spines of their target neurons (Somogyi *et al.*, 1983; Kisvárday *et al.*, 1985; Somogyi and Soltész, 1986). There are indications that further types of GABAergic neuron may also exist (Houser *et al.*, 1984; Somogyi, 1986) but the synaptic targets of these neurons have not been examined quantitatively.

GABA content of nonpyramidal cells in man

Human cortical grey matter contains about 10–30 nmol of GABA per mg protein (Perry *et al.*, 1984), and both GAD (Schlander *et al.*, 1987) and GABA (Schiffmann *et al.*, 1988) have been demonstrated immunohistochemically in neurons of human cortical samples. The present study extends these reports by identifying GABA-containing cells with distinct axonal and dendritic arborizations.

Bitufted cells similar to the GABA-positive ones shown in this study appear in many classical Golgi descriptions (Ramón y Cajal, 1899, 1909; Poljakov, 1953; Shkolnik-Jarros, 1962; Seldon, 1981; Meyer, 1987). It is clear that the axonal arborizations of these neurons can have distinct forms suggesting that according to their output, bitufted cells can play different roles in the cortex. For example, the most selective cortical GABAergic neuron the chandelier cell with its terminal axon segments wrapping around the axons of pyramidal cells usually exhibits a radially orientated bitufted dendritic arbor both in animals (Szentágothai and Arbib, 1974; Fairén and Valverde, 1980; Somogyi *et al.*, 1982), and particularly in man (Kisvárday *et al.*, 1986*a*; De Carlos *et al.*, 1987; Marin-Padilla, 1987). However, practically identical dendritic arbors can be found in cells with narrow radially orientated horse tail-shaped axons (Ramón y Cajal, 1899; Szentágothai, 1969, 1973; Valverde, 1978; Meyer, 1983; Somogyi and Cowey, 1981). In the monkey's striate cortex at least 5 types of neuron showed bitufted dendritic patterns in the deep layers (Lund, 1987; Lund, *et al.*, 1988) and others have been shown in the superficial layers (Lund, 1973; Tömböl, 1978; Somogyi and Cowey, 1981; Valverde, 1986). Because of the variety of axonal patterns it has been suggested that the descriptive name 'double bouquet' cell originally used by Ramón y Cajal (1899, 1909) to refer to both dendritic and axonal patterns is reserved for cells with the narrow radial axon bundle (Somogyi and Cowey, 1981). Our sample of bitufted neurons included cells with relatively small axons and although many collaterals had a predominantly radial course, no definite subclasses could be identified. The similarity of dendritic patterns presumably shows common inputs.

Multipolar or stellate cells with smooth or sparsely spiny dendrites do not differ markedly in the human cerebral cortex from various neurons described in other species (*see* Szentágothai, 1973; Jones, 1975; Fairén *et al.*, 1984; Peters and Saint Marie, 1984). The GABA-positive multipolar cell category also exhibits large variation in soma size and dendritic pattern. In the deep layers the size of the cell bodies increases noticeably, with large multipolar stellate cells in layers V and VI which are similar in size to those multipolar cells described in the cat (Meyer, 1983; Kisvárday *et al.*, 1987), monkey (Lund, 1973, type I cells of Jones, 1975; Szentágothai, 1975; DeFelipe *et al.*, 1986) and man (Marin-Padilla, 1969; Marin-Padilla and Stibitz, 1974; Meyer, 1987) as basket cells. Although the initial axon segments of these large stellate cells were clearly visible, the axons could not be revealed by impregnation, indicating that these cells have myelinated axons. Basket cells have indeed been shown to contain GABA and to have large diameter myelinated axons in the visual cortex of the cat (Somogyi *et al.*, 1983; Kisvárday *et al.*, 1987). The difficulty of relating the smaller GABA-positive multipolar cells to particular classes of neuron is again a consequence of the lack of knowledge about input/output criteria, e.g., their synaptic targets.

Neurogliaform or spiderweb cells can be recognized and they were named so by Ramón y Cajal (1899) who called them 'cellules neurogliforme', or 'araneiforme' because of their distinctive dendritic and axonal arborization. Recently Meyer (1987) described them in the human motor cortex. Here we provide evidence that they are GABAergic. Similar cortical cells have been described as 'type 5 cells' (Jones, 1975), 'neurogliaform cells with dense dendritic arborisation' (Szentágothai, 1973) and 'spine-free stellate neurons type d' (Lund *et al.*, 1981) in primates, 'smooth spherical multipolar neurons' (Peters and Regidor, 1981) and 'multipolar neurons of layers II-V with neurogliaform axonal plexus' (Meyer, 1983) in the cat. While Cajal's original terms illustrate the appearance of the cell vividly, the later used terms are somewhat cumbersome, therefore we refer to them simply as neurogliaform cells.

Recently Jones (1984) reviewed the literature on neurogliaform cells including the 'granular' or 'clewed cells' described by Valverde (1971) in layer IV of the monkey's striate cortex. However, this particular class of smooth dendritic cell has been shown to have properties distinct from the neurogliaform cells (Lund, 1973, 1987; Kisvárday *et al.*, 1986*b*). The most prominent feature of cells in layer IV is that the axons have large densely packed, bulbous boutons while neurogliaform cells have small and infrequent varicosities. The axons of cells in layer IV frequently contact somata while this has not been seen for neurogliaform cells. On the basis of the electron microscopic analysis of synaptic targets in both cat and monkey (Kisvárday *et al.*, 1985, 1986*b*) it has been shown that the particular type of cell in layer IV is a subclass of basket cells and we used the term 'clutch cell' to delineate these neurons (Kisvárday *et al.*, 1985, 1986*b*).

Role of GABAergic neurons

Physiological and pharmacological studies demonstrate an inhibitory effect of GABA on cortical cells (Krnjević and Schwartz, 1967; for review, *see* Krnjević, 1984). Depending on the site where GABA is released onto the postsynaptic cell, the inhibition probably has different effects on the information processing capacity of the cell (Blomfield, 1974; Koch *et al.*, 1982, 1983; Sillito, 1984). Thus it has been speculated that according to their axonal terminations, particular GABAergic cells play distinct roles in cortex (Martin, 1984; Somogyi and Martin, 1985). For example, termination on the axon initial segment of pyramidal neurons suggests GABAergic effects on the action potential generation and cortical output. Termination on the somata and proximal dendrites suggests an effect that is probably more graded than the former site but would still be relatively unselective, since inputs to most of the dendritic tree would be affected by somatic inhibition. In contrast, inhibitory input to distal dendrites would interact with other inputs arriving on the same dendrite only (Blomfield, 1974; Koch *et al.*, 1982, 1983). This could provide the basis for very selective inhibitory influences.

As predicted by light microscopic analysis, most types of cortical nonpyramidal cells do not seem to contribute to somatic GABAergic input (Somogyi and Cowey, 1981; Somogyi, 1986; DeFelipe and Fairén, 1988). For some nonpyramidal cells somatic termination was predicted, and subsequent electron microscopic analysis confirmed significant input to the somatic region of their target cells (DeFelipe and Fairén, 1982; Martin *et al.*, 1983; Kisvárday *et al.*, 1985). In the present study none of the 17 GABAergic cells that had impregnated axons seemed to terminate on the somata of cortical cells. This shows that the human cortex also has a large number and several varieties of cortical cells which contain GABA and which terminate on the distal regions of the dendritic tree. Indeed our electron microscopic analysis of GABAergic nerve terminals demonstrated that small dendritic shafts and dendritic spines are frequent targets of GABAergic synapses. These postsynaptic targets also received synapses from non-GABAergic boutons making type 1 synapses, many of which, such as those originating from thalamic and corticocortical cells, are known to be excitatory. The GABAergic terminals may be placed near the excitatory inputs to regulate their strength and temporal properties. Thus it is reasonable to assume that the inhibitory effect of neurogliaform cells would be selective on specific excitatory input(s).

The effect of GABA on the postsynaptic cells depends on the distribution of GABA receptors. Both GABA-A and GABA-B receptor binding sites have been demonstrated in human cortex (Chu *et al.*, 1987; Cross *et al.*, 1988), but their distribution on the postsynaptic cells is not known. High resolution immunocytochemical studies in other species (Somogyi *et al.*, 1989) and also in the human cortex (personal unpublished observations) show that the GABA-A/benzodiazepine receptor/chloride channel complex is localized not only at the synaptic junctions but also on the nonjunctional plasma membrane of neuronal somata, dendrites and dendritic spines. At first sight it appears paradoxical that GABAergic neurons are discriminating in their target selection with regard to the part of the neuronal surface that they innervate, while one of the receptors for GABA is distributed on the whole somatodendritic membrane. One way of resolving this paradox is by assuming that the density of receptors at the synaptic junction is not sufficient for achieving the required inhibitory effect in the full range of operation. At an increased level of excitatory input inhibition is increased by the increased release of GABA from synaptic terminals, and this could activate both junctional and nonjunctional receptors. This mechanism would ensure that the dynamic range of the neuron was kept in an optimal domain. The GABAergic terminals would need to be placed specifically in the appropriate positions to influence selectively only certain inputs.

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THE BULBOCAVERNOSUS REFLEX

A SINGLE MOTOR NEURON STUDY

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SUMMARY

Reflex latency variability was established for single motor neuron discharges in the bulbocavernosus reflex, as elicited by electrical stimuli to the dorsal penile nerve and recorded by a single fibre EMG electrode in the bulbocavernosus muscle. Whereas many reflex responses had a rather large latency variability of above 1000 μs (expressed as SD of mean latency) there was a group of motor neurons with a variability of around 500 μs. Single motor neuron reflex responses with shorter latencies tended to show less variability. No habituation of single motor neuron reflex discharges was observed on prolonged regular repetitive stimulation. Both absence of habituation and the relatively low latency variability of bulbocavernosus reflex responses for single motor neurons suggest similarities between this reflex and the first component of the blink reflex; we postulate that the shortest bulbocavernosus reflex pathway is oligosynaptic.

INTRODUCTION

The contraction of bulbocavernosus muscle or anal sphincter on penile squeeze (the bulbocavernosus reflex; Bors and French, 1952; Lapides and Bobbitt, 1956) indicates integrity of the reflex arc containing the sensory and motor fibres of the pudendal nerve and spinal segments S1–S4. Its electrophysiological correlate — using electrical impulses for stimulation and EMG techniques for recording the response — was described by Rushworth (1967) and later introduced into routine use in patients with suspected sacral neurogenic lesions (Ertekin and Reel, 1976). The bulbocavernosus reflex is usually included in textbooks under the 'exteroceptive' or cutaneomuscular reflexes and believed to be polysynaptic, a view held also by workers who have studied its behaviour more closely (Krane and Siroky, 1980; Varma *et al.*, 1986). In our previous electrophysiological studies we observed that the bulbocavernosus reflex shows little habituation and therefore postulated that it might have an oligosynaptic central integration (Vodušek *et al.*, 1983). The single fibre EMG (SFEMG) technique allows selective recording of single muscle fibre potentials, representing activity within single motor units and therefore discharges from single motor neurons. Such recordings make measurements of reflex latencies at the level of single motor unit responses possible. From repeated latency measurements (i.e., of consecutive reflex discharges) the latency variability of single motor unit reflex responses can be calculated and expressed, for

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instance, as the SD of the mean latency value. This latency variability has been correlated with the complexity of the reflex arcs of the H reflex (Trontelj, 1973), blink reflex (Trontelj and Trontelj, 1973), and the flexor reflex (Janko and Trontelj, 1983). The aim of this work was to study reflex responses of single bulbocavernosus motoneurons to electrical penile stimulation and to establish their latency variability, thus making comparisons with other better known reflexes possible. A preliminary report has already been presented (Janko and Vodušek, 1983).

SUBJECTS AND METHODS

Eleven male volunteers, recruited from patients with premature ejaculation, all of whom gave informed consent, participated in the study. They were aged 19–35 yrs, without evidence of neurological disease, and were not diabetic and did not take drugs. In the first 6 subjects a Medelec MS6 EMG machine was used for stimulation and recording; the measurements of reflex latency variability were mostly made off-line from tape. The recorder HP 3960 had — at high speed (15 ips) — a jitter that did not exceed 1–2 μs over segments of 10 ms. The measuring unit for latency variability consisted of a custom built 'jittermeter' (Trontelj *et al.*, 1979) and a computer (HP 2100S). In the rest of the study a Medelec-Vickers Mystro EMG system was used for stimulation, recording and analysis. The high-pass filters were set at 500 Hz and the low-pass filters to 16 and 20 kHz, respectively, on the MS6 or Mystro machine. The bulbocavernosus reflex was elicited electrically with ring electrodes (Disa 13L69) mounted on the penis. Direct responses were elicited by electrical stimulation of the pudendal nerve (branch) in the perineum (Vodušek *et al.*, 1983) with a bipolar surface electrode (Medelec TP NSP53054). Both reflex and direct responses were elicited with square wave pulses of 0.2 ms duration at a regular rate (0.5 – 2 Hz for the reflex and 2 – 5 Hz for the direct responses). Recordings were made with SFEMG needle electrodes (Medelec 53032) from single sites in bulbocavernosus muscles.

Muscle fibre potentials belonging to single motor units were sought, uncontaminated by firing of potentials belonging to other motor units. Repetitive reflex responses of particular single motor units were recognized as such by their constancy of shape. They were either single muscle fibre potentials (recognized according to established criteria; *see* Stålberg and Trontelj, 1979) or — even easier for identification — two or more muscle fibre potentials constituting a complex potential with time-locked spikes appearing according to the all-or-none principle with a small jitter between individual fibres (*see* Trontelj and Trontelj, 1973). Selective and reliable recording of such responses was made easier by accepting only recordings without interference from neighbouring motor units. The latter nearly always appeared at a different threshold, which made 'clean' recordings easier. For reflex latency variability measurements, a series of consecutive responses was sampled. As a rule two series of 50 responses were obtained for a particular motor unit. Recordings from the same bulbocavernosus muscle were accepted as belonging to a different motor unit if elicited at a different threshold value at a different needle electrode position. Up to 9 recordings from different motor units were obtained in a single subject, counting sites in both bulbocavernosus muscles. For both reflex and direct response analysis, latencies were measured automatically to a set point, adjusted manually on the steep slope of the spike potential. The accuracy of measurement for the two systems is stated as 1 μs for the jittermeter and 1/1000 of the time-base used for the Mystro. Mean latencies with SDs and ranges were calculated. As a rule two measurements were obtained. The SD of mean latency was taken as a measure of variability. If its values in repeated measurements differed by more than about 20% they were repeated; only recordings with a 'repeatable variability' were accepted. Recordings with the lowest latency variability were then included and are reported. Measurements of latency variability were also made for consecutive direct responses (muscle fibre potentials) from bulbocavernosus motor units. Direct responses were obtained with strong stimulation (*see* Trontelj *et al.*, 1986) of pudendal nerve (branches). Two series of 50 consecutive responses were sampled for each individual potential and the lower value is reported.

RESULTS

On increasing the strength of penile stimulation, responses from single motor units (*see* Methods) could easily be isolated with proper SFEMG needle adjustments. 'Threshold' stimulation was defined arbitrarily as the strength that elicited a response on about 90% of repetitive stimuli at a particular frequency of stimulation. Usually the responses from motor units emerged rather suddenly on threshold stimulation and then became regular (stimulus:response ratio 1) with very slight increases in strength. On further increases in strength, responses from other motor units often also appeared. On suprathreshold stimulation, individual responses could easily be followed for longer periods of time. We estimate that in some instances about 1000 consecutive repetitions of the same motor unit reflex response were obtained without any drop-outs.

The mean latencies of reflex responses of various motor units chosen for measurement ranged from about 29 to 45 ms. In 2 subjects motor unit reflex discharges could also be obtained and measured at a later latency interval between about 50 and 75 ms. The latencies of consecutive reflex responses showed some gross and some subtle latency changes. The gross changes consisted of a bimodal or polymodal distribution of response latencies; the response 'jumped' between these discrete latency values on consecutive discharges. Occasionally this was closely correlated with changes in the strength of stimulus applied, shorter latencies being obtained with stronger stimuli (fig. 1). In addition to this phenomenon a slight variability of latency could also be seen in case of responses

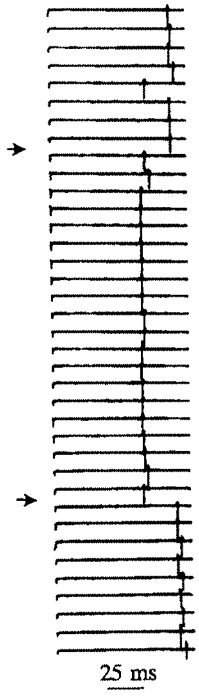

FIG. 1. Bulbocavernosus reflex response of a single motor neuron, as characterized by an individual muscle fibre action potential. Consecutive responses from above downwards. Stimulus intensity is increased at upper arrow and decreased again to the previous level at lower arrow. A discrete latency change can be seen on changing the stimulus intensity.

with a 'constant' latency. If in these cases latencies of consecutive reflex responses were plotted, they occasionally showed a somewhat fluctuating pattern of changes; nevertheless their frequency histograms showed a rather normal distribution.

With regard to reflex latencies and their variabilities the following observations were made. (1) Latencies could shorten by 'jumps' on increasing the stimulus strength (fig. 1). (2) A slight but significant decrease in latency was also observed on increasing stimulus strength in responses otherwise appearing at a 'constant' latency value (measurements made in 7 motor unit responses showed a mean shortening of the latency for 715 μs, as well as a mean decrease in reflex jitter for 317 μs; *see* fig. 2). (3) Some motor units occasionally discharged more than once in a particular reflex response; both a polymodal latency distribution as well as multiple discharges were occasionally observed for the same motor unit (fig. 3). (4) Response latencies from 4 motor units were measured separately at both an 'early' and 'late' discrete latency value which were 3–5 ms apart. Reflex responses showed less reflex latency variability at the 'early' latency value (444 ± 44 μs vs 1012 ± 138 μs). (5) Putting all measured minimal reflex latency variabilities of individual motor units together, a clear grouping could be seen. Motor units from the 'late' latency interval (between 50 and 75 ms) had a larger latency variability as

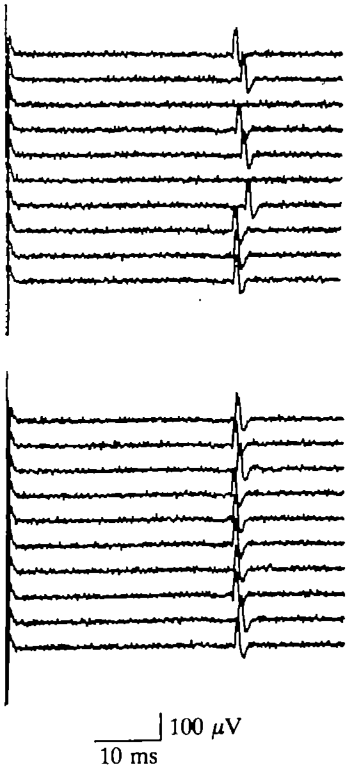

FIG. 2. Bulbocavernosus reflex response of a single motor neuron on threshold (*above*) and slightly suprathreshold (*below*) electrical stimulation. Consecutive responses always from above downwards. At threshold stimulation occasional failure of the stimulus to elicit a reflex response can be seen, as well as a greater variability of reflex latencies.

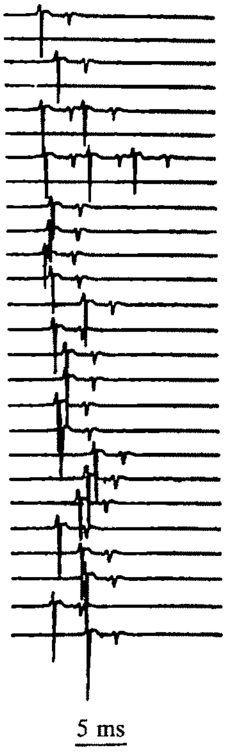

FIG. 3. Bulbocavernosus reflex response of a single motor neuron represented by a complex potential of 2 single muscle fibre action potentials belonging to this particular motor unit. Responses to consecutive stimuli from above downwards. The signal is delayed for 30 ms for clearer recognition. Double and triple discharges on individual electrical stimuli can be seen occasionally. Single discharges may occur at variable discrete latency values, which roughly correspond to latencies of individual discharges within a multiple discharge.

compared with those from the 'early' latency interval (between 29 and 45 ms). Even among the latter, those with short latencies tended to have less latency variability (fig. 4). The reflex latency variability of motor units from the 'late' latency interval was between 1706 and 10901 μs (7 measured motor units); for the motor units from the 'early' latency interval it was between 387 and 2151 μs (49 measured motor units). (6) There was a whole group of motor units among those appearing at the early latency interval which had a reflex latency variability around 500 μs (fig. 4).

To estimate the contribution of peripheral (also technical) factors to the reflex latency variability, the variability of latencies of direct responses in the bulbocavernosus muscle on pudendal nerve (branch) stimulation was also measured (fig. 4). In some measurements low jitter values (5 μs and below) were obtained and were discarded as they were believed to be due to direct muscle stimulation (*see* Trontelj *et al.*, 1986). The latency variability of direct responses ranged from 8 to 50 μs (mean 26,9 ± 10 μs; 33 measured motor units).

DISCUSSION

Latency variability of reflex responses recorded with surface electrodes reflects the variability of those motor units activated at the beginning of the reflex responses (Lloyd

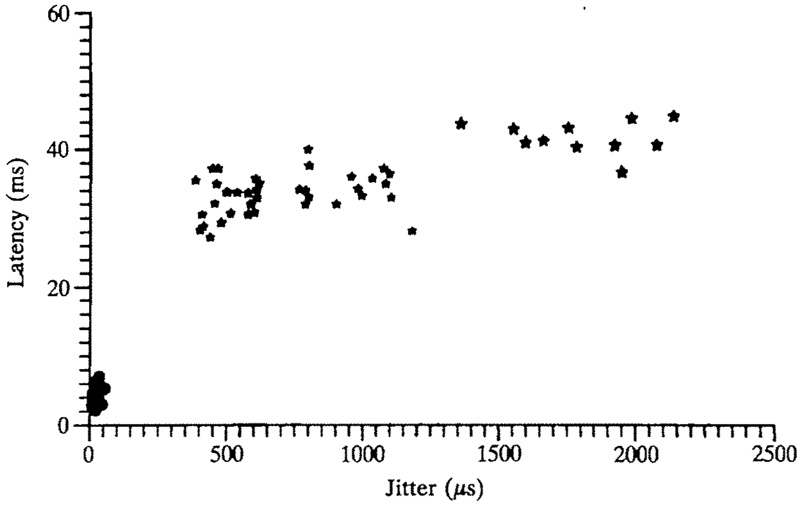

FIG. 4. Reflex latency variability of single motor neuron responses with latencies in the 'early' latency interval (stars) as well as variability of direct responses (filled circles, lower left).

and McIntyre, 1955; Rall and Hunt, 1956) and correlates with the complexity of their reflex arc (Penders and Delwaide, 1973). Recording with the single fibre EMG (SFEMG) technique allows for selective observation of single motor neuron reflex discharges in humans (by detecting single muscle fibre potentials, which are marking individual motor unit behaviour). Trontelj (with coworkers) pioneered this research, measuring the reflex latency variability of the H reflex (Trontelj, 1968), the first and second components of the blink reflex (Trontelj and Trontelj, 1973) and the flexor reflex (Janko and Trontelj, 1983). Reflex latency variability must of course involve both 'central' factors (variability of synaptic delay, etc.) as well as 'peripheral' factors (variability at stimulation site, the neuromuscular transmission, etc.). The peripheral factors, however, can be estimated by measuring the latency variability of electrically elicited direct responses in the same muscle. Thus Trontelj and Trontelj (1973) were able to show that the latency variability of reflex motor neuron responses in the first component of the blink reflex was 25.5 times the latency variability of their direct responses. Our measurements give a value of about 20 times greater variability for the most stable bulbocavernosus reflex responses, as compared with latency variability of direct responses in the bulbocavernosus muscle. We can also compare the bulbocavernosus reflex latency variability with the latency variability of the monosynaptic H reflex. Its latency variability (expressed as SD of mean latency) was shown to be ~150 μs (Trontelj, 1973), which makes the bulbocavernosus latency variability ~3 times greater. This relatively 'small' variability of bulbocavernosus reflex responses in the shorter latency range is quite unlike the typical large latency variability of polysynaptic reflex responses, for instance for single motor neuron responses in the second component of the blink reflex (Trontelj and Trontelj, 1973) or the flexor reflex (Janko and Trontelj, 1983). Such 'large' latency variability (i.e., above 10 times H reflex latency variability) was recorded for bulbocavernosus reflex responses in the 'late' latency interval. The latency variability for these late reflex responses is actually underestimated in our study as responses with obviously large latency variability were not selected for measurement. Some motor neuron responses from the 'early' latency range in the bulbocavernosus reflex also showed such larger latency variability (and tended to have relatively longer mean latencies as the more stable responses). Such motor neurons also often showed a bimodal or polymodal distribution of reflex response latencies. A likely explanation of polymodal latency distribution of reflex responses as well as of multiple discharges of the same motor neuron in a reflex response is conduction through alternative interneuron pathways including a different number of interneurons. This would also explain the relatively larger latency variability of the motor neuron response appearing at the later latency value in a response with a bimodal latency distribution. Similarly, the relatively larger latency variability of bulbocavernosus reflex responses with longer latencies is probably reflecting additional interneurons in their reflex arcs. There was also a correlation between the stimulus strength and the reflex latency variability, the latter being decreased by an increase in stimulus strength. This could be accounted for by an increase in steepness of the excitatory postsynaptic potentials, caused by spatial facilitation (depolarization of more afferents on stronger stimulation).

An interesting comparison can be made with the reported latency variability of responses in the levator ani obtained by intramuscular electrical stimulation (Trontelj *et al.*, 1974): they observed direct, recurrent, and reflex responses. The latter had latencies between about 27 and 85 ms, and their latency variabilities were grouped around the values 155 μs, 550 μs, 1200 μs and 2300 μs. These latency variability values (and therefore the complexities of the respective reflex arcs) were compared by the authors with the H reflex, and the first and the second components of the blink reflex, respectively. In our study of the bulbocavernosus reflex latency variability we clearly could not obtain values close to 'H reflex' latency variability as no muscle afferents were stimulated. However, the other values correspond remarkably well; this further strengthens our opinion that identical reflex responses can actually be obtained in any perineal or pelvic floor muscle on stimulation of sacral somatic afferents (Vodušek *et al.*, 1983).

Many hundred consecutive reflex discharges of individual motor units on regular repetitive weak suprathreshold stimulation in this study show absence of habituation in the bulbocavernosus reflex pathway. Absence of habituation is well known for the first component of the blink reflex and was taken by Rushworth (1967) as an argument against the polysynaptic nature of that reflex pathway. Trontelj and Trontelj (1973) convincingly argued that the reflex arc of the first component of the blink reflex is oligosynaptic. As already discussed, the early bulbocavernosus reflex responses similarly show (1) a comparable ratio of reflex versus direct response latency variability; (2) a comparable ratio of H reflex versus bulbocavernosus reflex latency variability; and (3) absence of habituation. We therefore postulate that the first component of the bulbocavernosus reflex, which is by common assumption usually referred to as a polysynaptic cutaneomuscular reflex, in fact has an oligosynaptic reflex pathway.

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OCULOMOTOR DISTURBANCES DURING VISUAL-VESTIBULAR INTERACTION IN WALLENBERG'S LATERAL MEDULLARY SYNDROME*

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SUMMARY

Transient and lasting oculomotor disturbances during visual-vestibular interaction are described in 9 patients with Wallenberg's lateral medullary syndrome. In all patients magnetic resonance imaging (MRI) demonstrated a single focal area of pathological signal intensity in the (dorso)-lateral medulla suggesting infarction. In 2 of these 9 patients and in 3 further patients with no medullary signs, the infarction involved the cerebellar territory of the posterior inferior cerebellar artery (PICA). Acutely, all patients with Wallenberg's syndrome (except 1) had saccadic lateropulsion and spontaneous nystagmus in light with the horizontal fast component beating to the contralateral normal side. The velocity of the slow drift to the side of the lesion was dependent on eye position and induced a characteristic asymmetry of the visually and vestibularly elicited slow eye movements. In most patients smooth pursuit, optokinetic nystagmus and visual suppression of the vestibulo-ocular reflex were still impaired when this spontaneous drift was minimal or absent. The oculomotor disturbances in patients with and without cerebellar infarction are compared. The following conclusions are made. (1) The spontaneous drift that is dependent on eye position is mostly created by 'ocular lateropulsion', that is, a tonic bias within the oculomotor system which may have several sources. (2) The abnormalities and asymmetries of oculomotor responses during visual-vestibular stimulation cannot solely be explained by this spontaneous drift and its interaction with otherwise normal eye movements. Instead, structures and pathways are damaged in Wallenberg's syndrome which mediate visual and/or motor signals important for the cerebellar control of visually-guided slow eye movements. (3) Damage to these pathways occurs in the lateral medulla, as the MRI findings show that in most patients the cerebellum is rarely involved, but no definite conclusion can be made as to which of the fibres travelling in the inferior peduncle to the cerebellum may be interrupted.

INTRODUCTION

The lateral medullary (retro-olivary) or Wallenberg's syndrome is a unique, although variable, neurological entity. Its cause is most often ischaemia in the territory of the posterior inferior cerebellar artery which also supplies the posteroinferior cerebellum. Some signs such as Horner's syndrome, dysphagia and crossed sensory loss are readily explained by damage to nuclei and fibre tracts in the lateral medulla (Currier *et al.*, 1961). The pathophysiological mechanisms and anatomical correlations of the many and complex oculomotor disturbances are, however, not obvious, but involvement of the cerebellum and/or caudal part of the vestibular nuclei is assumed to be of major

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* To Professor G. Baumgartner on his 65th birthday.

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importance. A characteristic denominator of the disturbances in oculomotor performance is directional preponderance of the saccadic and slow eye movements to the side of the lesion (Kommerell and Hoyt, 1973; Baloh *et al.*, 1981; Kirkham *et al.*, 1981; Estañol and Lopez-Rios, 1982). It is not clear, however, whether this directional preponderance simply reflects an imbalance or bias within the oculomotor system, also called 'ocular lateropulsion' (Kommerell and Hoyt, 1973), or whether the oculomotor abnormalities also reflect damage to pathways which mediate sensory and/or motor signals essential to the cerebellum for the control of visually-guided eye movements. The origin of the imbalance is also not well understood and, furthermore, an immediate clinicoanatomical correlation was not possible in previous studies. Magnetic resonance imaging (MRI) is now able to delineate hindbrain infarctions precisely enough to allow a correlation between involvement of the lateral medulla and/or cerebellum and clinical signs (Kistler *et al.*, 1984; Bogousslavsky *et al.*, 1986; Ross *et al.*, 1986). To explore these problems further we repeatedly examined the eye movements during visual-vestibular stimulation at the bedside and electro-oculographically in 9 selected patients with clinically and radiographically localized lesions in the lateral medulla, and in 3 further patients with cerebellar but no medullary infarction.

PATIENTS AND METHODS

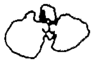
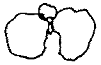
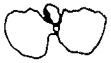
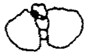
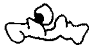
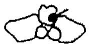
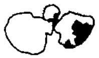
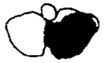
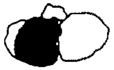
Twelve out of 19 patients referred to the Department of Neurology because of the acute onset of dizziness, vomiting and gait difficulty are reported in this study. In these 12 patients, eye movement abnormalities were marked and MRI (*see below*) allowed localization of the underlying pathology. In 9 patients (Cases 1–9, Table 1), Horner's syndrome, dysphagia and crossed sensory disturbances suggested Wallenberg's lateral medullary syndrome, most probably due to infarction. The symptoms in Cases 10–12 were initially believed by the referring physician to be caused by an acute episode of a peripheral vestibular disturbance, but CT scanning revealed cerebellar infarction (Huang and Yu, 1985). The remaining 7 patients not reported in this study also had an acute Wallenberg's syndrome. In 4, eye movements were disturbed but MRI was normal. In the other 3, MRI readily visualized the lesion in the lateral medulla but eye movements were normal. The salient signs and symptoms of the 12 patients participating in this study are summarized in Table 1. Most patients had one or several identifiable predisposing factors for vascular disease (hypertension, diabetes mellitus). Mean age of the 2 females and 10 males was 55 (range 36–75) yrs.

Oculomotor examination

Saccadic and slow eye movements were carefully tested using bedside methods. Several days after the onset of symptoms horizontal and vertical eye movements were recorded (Table 1) with conventional d.c.-coupled electro-oculography (EOG). Signals were low-pass (30 Hz cut-off frequency) filtered. Patients did not wear their corrective glasses during testing, and night sedation was discontinued the day before EOG recordings. All patients (except Case 1) were reexamined 3–21 months later (Table 1).

Horizontal and vertical saccades were made spontaneously and on command in darkness and in response to step displacement (10° to 40° from the primary position) of a small target light at a distance of 65 cm. Eye movements were calibrated before each trial, at intervals of approximately 60–120 s. Sinusoidal and ramp movement of the fixation light in a darkened room induced *predictable* horizontal smooth pursuit (SP) eye movements. Periods were between 1.5 and 6 s and amplitudes were between 15° and 35°, covering a range of peak velocities from 7 to 90 deg/s. Optokinetic responses (OKN) were elicited with a full-field visual surround moving at constant velocities between 20 and 100 deg/s. Instructions were aimed at obtaining a 'look' type of OKN. Peak velocity of the visual stimulus during SP and OKN was within ±5% of the

TABLE 1. CLINICAL FEATURES, MRI ABNORMALITIES (LEVEL WITH THE MOST EXTENSIVE PATHOLOGY) AND TIME OF EOG RECORDINGS

Case	Age (yrs)	Sex	Nausea, imbalance	Horner's syndrome, ipsi	Dysphagia, hoarseness	Decrease in pain, temperature sensation		Limb ataxia ipsi	MRI lesion	EOG	
						Face ipsi	Body contra			Acute (day)	Follow-up (months)
1	75	M	++	Yes	++	+	+	+		10th	–
2	73	M	+	Yes	+	–	(+) (and face)	–		3rd, 7th	3
3	46	M	++	Yes	+	+	+	+	Fig. 1a–c	7th	12
4	68	M	++	Yes	+	+	+	+		5th, 8th, 14th	4, 6
5	36	M	++	Yes	++	+	++	++		8th	3, 6
6	39	F	+	Yes	–	+	+	–		7th	3
7	54	F	+	Yes	+	+	+	(+)		–	4
8	46	M	++ Somnolent	Yes	++	+	+	++	Fig. 1d–f	–	19,20
9	51	M	++	Yes	–	+	+	++		7th, 14th	6
10	46	M	++	No	–	–	–	–	Fig. 1g–i	5th	6
11	67	M	++	No	–	–	–	(+)		6th	5
12	60	M	++	No	–	–	–	–		19th	4

ipsi = ipsilateral; contra = contralateral; ++ = severe; + = moderate; (+) = slight; – = no deficit.

expected value. The horizontal vestibulo-ocular reflex (VOR) was induced by rotating the patient in darkness on a human turntable with the head secured. Sinusoidal rotations were at periods between 3 and 5 s and with amplitudes between 20° and 40°. Patients were instructed to make numerical counts. VOR testing immediately followed VVOR testing, i.e., rotation of the patient in front of a space-stationary fixation light which he had to track (visuovestibulo-ocular reflex). Visual cancellation of the VOR (VOR suppression) was tested with the target light attached to the drum which was coupled to the chair. Peak velocity of the vestibular stimulus was within ±7% of the expected value. All patients were informed about the purpose of the examination and that they could refuse it.

Analysis

Data were written out on a six-channel rectilinear oscillograph. Eye velocity was measured from chart recordings by evaluating the hand-drawn slopes of the eye position trace in an interval with no catch-up saccades. For calculating the gain as the ratio of peak slow eye to peak stimulus velocity the 5–10 trials with the *best* performance were selected. SP eye movements were tested at 3–6 different stimulus velocities. For reasons of simplicity, the values for stimulus velocities between 18 and 30 deg/s, 47 and 63 deg/s, and 75 and 90 deg/s were pooled and displayed in the figures at a stimulus velocity of 25, 55 and 80 deg/s, respectively. The amount of visual suppression of VOR is expressed as

$$\left[1 - \frac{\text{VOR gain during suppression}}{\text{VOR gain}}\right] \times 100\%$$

Normative values were obtained from 10 normal subjects comparable in age, mean age 54 (range 40–74) yrs, to that of the patients. Control values are similar to those reported in the literature for comparable stimulus conditions (Barr *et al.*, 1976; Chambers and Gresty, 1983). VOR gain is between 0.85 (SD ±0.14) at 32 deg/s and 0.83±0.11 at 84 deg/s; VVOR gain ranges between 1.01±0.03 at 32 deg/s and 0.99±0.03 at 84 deg/s. SP gain is between 0.96±0.07 at 25 deg/s and 0.88±0.07 at 80 deg/s. The VOR is visually attenuated during VOR suppression by more than 95%. OKN slow phase velocity gain is 0.94±0.02 at a stimulus velocity of 40 deg/s and 0.85±0.05 at a velocity of 80 deg/s.

MRI studies

These were performed not earlier than 4 days but within 3 wks after onset of symptoms on a 1.5 Tesla scanner (Philips Gyroscan). MRI was repeated in 3 patients: in Cases 5 and 10 at 8 months and in Case 10 20 months after infarction. Axial scanning planes were in an orientation corresponding to the CT brain anatomy, i.e., sections in the transverse plane oriented 10–20° frontal up from Reid's anatomical baseline. In all patients axial T_2-weighted images were performed with spin-echo pulse sequences (TR 1800–2200; TE 50 and 100 ms). Areas with prolonged T_2 suggesting structural lesions will show a high signal intensity. T_1-weighted images (spin-echo; TR 500-550, TE 20–30 ms) were undertaken in 7 patients. Six patients had additional sagittal and 3 patients coronal images. Slice thickness was between 5 and 6 mm with a 1 mm gap between sections. The image matrix was 256×256, the field of view 200–210 mm.

RESULTS

Magnetic resonance imaging

In all 9 patients with a lateral medullary syndrome a single focal area of increased signal intensity of variable size was visualized in the dorsolateral medulla oblongata in T_2-weighted axial images suggestive of infarction (Cases 1–9, Table 1; fig. 1A–F). In 2 patients this area was also identified in sagittal sections. We were unable to determine precisely and with confidence the rostrocaudal and dorsoventral extension of these areas

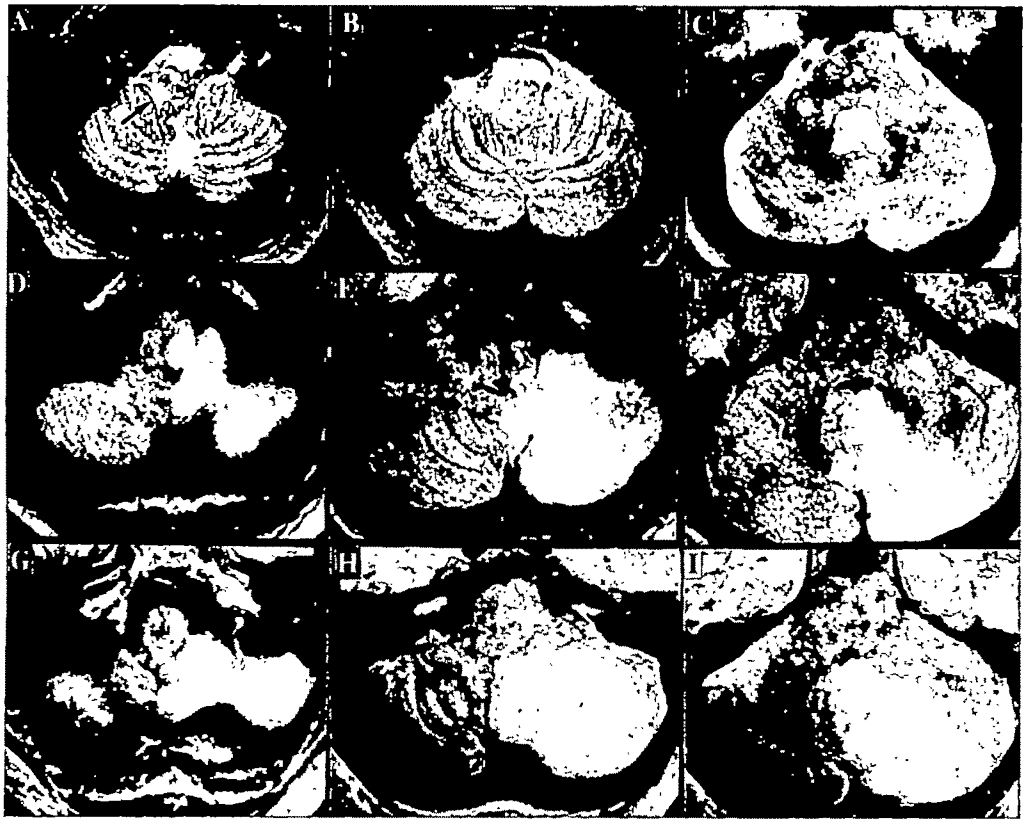


FIG. 1. Axial MRI at 3 different levels through the lower medulla and suboccipital cerebellar surface (A,D,G) up to the level of the dentate nuclei (C,F,I) in *Cases 3* (A–C), *8* (D,F) and *10* (G–I). T_2-weighted sequences (TR 2000 ms, TE 100 ms in A–C; CSF has the same increased signal intensity as the lesion. TR 1800 ms, TE 50 ms in D–F; TR 2020 ms, TE 40 ms in G–I). The areas of increased signal intensity in the right lateral medulla (black arrow in A), in most of the left medulla (D) and in the left posteromedial cerebellum (D–I) are compatible with infarction. Note compression of the fourth ventricle and shift of cerebellar midline in *Case 10* (H,I).

in relation to other structures such as the inferior olive, the caudal vestibular nuclei and the cranial nerves IX and X. In Case 8, with the most extensive lesion, it probably involved the caudal vestibular nuclei and the inferior olivary nucleus (fig. 1D). In only 2 of these 9 patients (Cases 8,9) was the cerebellum also involved (fig. 1D–F). In Cases 10–12 who also experienced the acute onset of dizziness, vomiting , and severe imbalance but who had no localizing medullary signs, the posteromedial cerebellum but not the lateral medulla showed an abnormal signal intensity (fig. 1G–I). Thus imaging demonstrated, in Cases 8–12 but not in Cases 1–7, infarction in the cerebellar territory of the posterior inferior cerebellar artery (PICA). The cerebellar lesions in Cases 8 and 10–12 were comparable and extended to the entire cerebellar territory of the PICA (fig. 1D–I; Table 1) involving the tonsil (D,G) and the nodulus and uvula (E,F,I). In Case 9, infarction in the cerebellum was limited to the posterior part of the hemisphere, sparing the vermis and the tonsil (Table 1). Infarction was haemorrhagic in Cases 11 and 12. In 2 patients (Cases 8,9) a mass of increased signal intensity was visualized within the lumen of the vertebral artery on the side of the lesion, suggesting severely reduced blood flow or even occlusion by thrombus; and in 3 other patients (Cases 3,4,5) the lumen of the vertebral artery was visualized on the normal side only.

MRI was repeated in Case 8 at 20 months and in Cases 5 and 10, 8 months after the acute onset of symptoms. T_1-weighted images demonstrated severe atrophy of the posteromedial cerebellum in Cases 8 and 10. The posterolateral recess of the fourth ventricle was enlarged, but it was difficult to estimate to what extent the ipsilateral nodulus and uvula had been damaged. The region of the flocculus appeared normal. The dentate nucleus on the side of the lesion was about half its normal size (in T_2-weighted images). In Case 8, the majority of the left medulla was severely atrophic. In Case 10 the medulla was unremarkable. In Case 5 T_1-weighted transverse images demonstrated a low-signal intensity zone in the lateral medulla compatible with old infarction.

In summary, all patients selected for this study had abnormal MRI findings. We believe that MRI is highly accurate in excluding or establishing infarction in the cerebellar territory of the PICA. It is, however, rather difficult to delineate precisely the borderzone of the infarction either in the acute or chronic stages, and to be certain about the extent of damage suffered by medullary and cerebellar structures.

Saccadic lateropulsion

Saccadic lateropulsion, defined as an asymmetry of saccadic amplitudes despite full movement range (Baloh *et al.*, 1981), was obvious at the bedside and electrooculographically in 8 of the 9 Wallenberg patients (except Case 6). Most consistently, saccades to the normal side were of small amplitude and multiple saccades were needed to look away from the side of the lesion. Visually guided saccades to the damaged side were usually of normal amplitude; in 4 patients, however, saccades were regularly hypermetric. The quick phases of optokinetic and vestibular nystagmus had also asymmetric amplitudes so that those directed away from the lesion were smaller than those towards the lesion. Cases 10−12 with a cerebellar but no medullary infarction had normal and symmetric spontaneous and visually guided saccadic eye movements and nystagmic fast phase amplitudes.

Saccadic hypometria was most prominent in Wallenberg's patients when the eyes were tonically deviated in darkness towards the lesion side and a fixation light was unexpectedly presented in midgaze position (upward arrow in fig. 3E). The target light was fixated (in fig. 3E from an eye position of approximately 40° on the lesion side) with multiple small saccades (oblique arrow). Cases 4 and 5 who were evaluated quantitatively needed on average 890 ± 405 ms (SD) (latency not included; $n = 26$) to foveate the fixation light from an eye position of $23.0 \pm 6.5°$ on the lesion side. During this period they made 6.3 ± 3.1 saccades, the largest of which had an amplitude of $10 \pm 4.3°$. This amounts to 43% of the total displacement. However, larger saccades away from the lesion side were possible in response to step displacement of the fixation light (fig. 3A) or when making voluntary saccades in darkness (with or without blinks) (fig. 2B). The same 2 patients needed only 2.5 ± 0.9 saccades (n = 27) with a maximal amplitude of 27 ± 4.0° and 260 ± 104 ms (latency not included) to refixate the target light when it was displaced by 40° away from the lesion side regardless of initial eye position. The mean amplitude of the largest saccade was 67% of the total displacement. Even larger saccades were made on command in darkness away from the lesion side with an amplitude of 52 ± 20.5° (fig. 2B). Case 9 showed similar, albeit less marked, task-dependent differences in saccadic hypometria.

Saccadic lateropulsion persisted in 3 patients either with (Case 8) or without cerebellar infarction (Cases 4,5) and in the absence of spontaneous drift and tonic deviation (Cases 5,8). In Case 4 the eyes still deviated in darkness with a staircase sequence of small saccades towards the lesion side (*see below*; fig. 2D). In Cases 5 and 8 visually guided saccades towards the lesion side were hypermetric and those towards the normal side hypometric, but occasionally in Case 8 also hypermetric. In Case 4 visually guided saccades to the lesion side were of normal amplitude but those towards the normal side were regularly hypometric. In all 3 patients the amplitude of fast phases of VOR and OKN were strongly asymmetric, being much smaller to the normal side. Often the fast phase amplitudes were so small that a shimmering-like vestibular nystagmus was generated in response to rotation to the normal side.

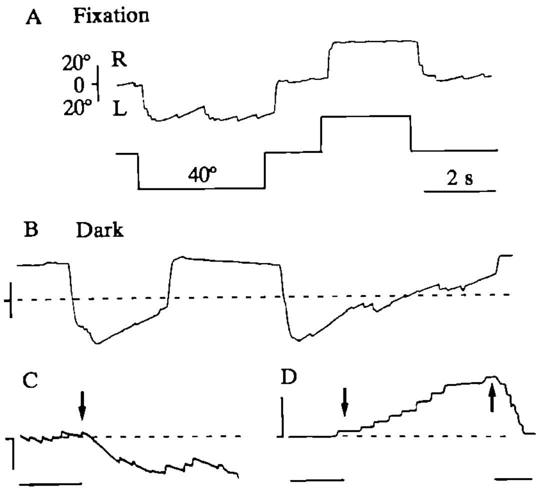


FIG. 2. A,B, horizontal eye movements in *Case 5* with a right-sided infarction in the dorsolateral medulla. In A, fixation of a single light point in midgaze and 40° lateral positions. In B, the patient is in darkness and is asked to shift gaze rapidly between extreme right (upward deflection) and left (i.e., normal side, downward deflection) positions. The midgaze position is indicated by the dashed line. C, after extinction of the fixation light in midgaze position (downward arrow) the eyes in *Case 9* deviate to the side of the lesion (7th day). D, 6 months after right-sided infarction in *Case 4* the eyes still move in darkness towards the side of the lesion with small saccades.

In summary, lateropulsion of horizontal saccades was observed in patients with lateral medullary infarction but not in those 3 patients with a cerebellar infarction. The amount of hypometria to the normal side was task-dependent (Kommerell and Hoyt, 1973; Kirkham *et al.*, 1981). Dysmetria of visually guided saccades and asymmetry of fast phase amplitudes of VOR and OKN could persist in the absence of spontaneous drift and tonic deviation.

Skew deviation

Six of the 9 Wallenberg's patients but not Cases 10–12 complained of double vision mainly on looking to the side of the lesion. They had skew deviation with abduction hypotropia of the ipsilateral eye. In Case 8 skew deviation persisted with double vision when looking to the lesion side.

Spontaneous drift in light and darkness

Acutely at the bedside, all patients with Wallenberg's syndrome (Cases 1–9) had spontaneous nystagmus of variable intensity in midgaze position in light with the head erect. Its horizontal fast component was directed to the intact (=contralateral) side. It also had a torsional and in 4 patients an upward component. In none of the patients did the horizontal component reverse in direction under Frenzel glasses or in darkness. The intensity of the horizontal component typically increased on contralateral gaze, i.e., with eye positions in the fast phase direction, and decreased on ipsilateral gaze. This decrease in the horizontal component was often accompanied by an increase in the vertical component.

Horizontal drift was still prominent at the time of recording in 4 patients (Cases 3–5,9; recorded between days 5 and 8). As shown in fig. 2A,B (Case 5), fig. 3A,E (Case 4), and fig. 5A (Case 9), the velocity of the drift was strongest when the patient was looking to the normal side, and there was always a gaze region on the lesion side where horizontal drift was minimal or absent. Without fixation the eyes moved smoothly towards the lesion side, occasionally interrupted by resetting saccades (fig. 2B). A nystagmus-like pattern appeared when the patient was enforced to maintain his gaze in certain positions. The velocity of the drift between two resetting saccades in darkness had a linear or an exponentially decreasing profile (fig. 2B,C). On ipsilateral eccentric gaze drift direction reversed (figs. 2A,B, 3A). With fixation in midgaze position the horizontal drift component directed to the lesion side in the 4 patients had a mean velocity of 5.3 ± 4.2 deg/s. The velocity increased to 10.9 ± 2.4 and 12.9 ± 3.2 deg/s on 20° and 40° contralateral gaze, respectively. It decreased to 1.6 ± 2.8 deg/s on 20° ipsilateral gaze, and it reversed direction on more eccentric gaze so that it was directed to the normal side with an average velocity of 6.4 ± 3.4 deg/s on 40° ipsilateral gaze. When the fixation light in midgaze position was switched off, the eyes drifted (often with a downward component) towards the lesion side (fig. 2C). This drift was interrupted by small saccades either in or against drift direction. On average, the eyes moved within 2.8 ± 0.9 s (range 1.2–3.7 s) from midgaze position to a position of 19 ± 2.1° on the lesion side where drift was minimal. The ratio of the drift velocity during fixation in midgaze position and the peak velocity with which the eyes moved smoothly towards the lesion side immediately after the fixation light had been switched off was 0.52 ±0.22. This indicates that drift velocity was reduced by fixation (fig. 2c). Similarly, drift velocity was most prominent for a period of 1–2 s after fixation had been interrupted by a fast gaze shift (fig. 3A). The tendency of the eyes to deviate to the lesion side was also obvious during visual suppression of the vestibulo-ocular reflex when fixation was rendered more difficult by the concomitant vestibular drive to the lesion side, and when the patient was put into darkness during sinusoidal rotation (*see below*, fig. 3D).

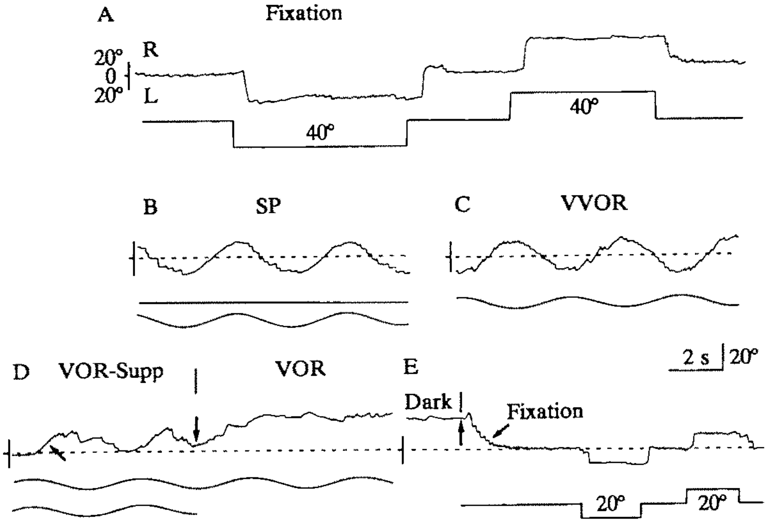


FIG. 3. Horizontal eye movements in *Case 4* with right-sided medullary infarction 5 days after the onset of symptoms. A, during fixation of the target light in midgaze position and in a position 40° lateral to it. B, during sinusoidal smooth pursuit (4 s ± 15°). C, during visuovestibular interaction (4 s ± 20°). D, during visual suppression of the vestibulo-ocular reflex (VOR-Supp) and during VOR in darkness (downward arrow marks extinction of fixation light). E, with the patient in darkness the target light is unexpectedly turned on for fixation in midgaze position (upward arrow); first trace, horizontal eye position; second and third traces, position of chair and of fixation light respectively. An upward deflection in all traces corresponds to a movement to the right (R) which is the lesioned side. Dashed line marks midgaze position.

Cases 10–12, with cerebellar infarction only, had no spontaneous nystagmus during fixation in midgaze position but post-headshaking nystagmus to the lesion side (Cases 10,12) or normal side (Case 11). These patients were seen by us relatively late, 4, 6 and 18 days after the onset of symptoms, thus a transient spontaneous nystagmus immediatey after the infarction cannot be excluded.

None of the patients showed persistent spontaneous nystagmus in midgaze position with the head erect in light or darkness. In most patients, however, there was a slight centripetally directed drift on extreme (ipsilateral and/or contralateral) eccentric gaze. This gaze-evoked drift was most prominent in Case 8. It appeared in light at a gaze angle of approximately 20° to either side. The velocity of the drift had an exponentially decreasing profile. This patient also had rebound nystagmus which was more prominent after looking towards the normal side. All other patients, including Cases 10–12, had no rebound nystagmus. Case 4 was the only patient in whom the eyes, after 6 months, still deviated towards the lesion side in darkness. After extinction of the fixation light in midgaze position the eyes moved within 2.5 ± 0.7 s by $23.5 \pm 3.2°$ to the side of the lesion. Interestingly, the eyes did not move, as they did in the acute stage, by a combination of slow (drift) and fast movements but exclusively by small saccades in a staircase sequence with no drift in the intersaccadic interval (fig. 2D). Furthermore, on ipsilateral gaze microsquare wave jerks appeared.

In summary, spontaneous nystagmus to the normal side is a prominent sign in the acute lateral medullary syndrome. The horizontal drift velocity directed towards the side of the lesion was influenced by different eye positions and by fixation. Drift velocity was faster on contralateral than ipsilateral gaze, and without than with fixation. In none of our patients did drift velocity reverse its direction in darkness except on extreme ipsilateral gaze. The resetting saccades of the spontaneous nystagmus seemed to be triggered rather by the effort to hold the eyes in a certain position than by the drift itself. Horizontal drift to the side of the lesion may be consequent on the tendency of the eyes to deviate tonically to the side of the lesion. This pulling force or 'lateropulsion' acts on the oculomotor system, forcing the eyes to move slowly and occasionally also rapidly with small saccades towards a region on the side of the lesion where this force is absent. Signs of 'ocular lateropulsion' were not observed in patients with infarction in the cerebellar territory of the PICA.

Slow eye movements and their interaction with spontaneous drift

Figs 3B–D and 4 demonstrate in 1 patient (Case 4) the characteristic disturbances of the visually and vestibularly induced slow eye movements with their directional preponderance to the side of the lesion when spontaneous drift is prominent. Such a directional preponderance was observed acutely at the bedside in almost every patient with Wallenberg's syndrome. Case 5 was an exception. Smooth pursuit (SP) is normal or even too fast towards the lesion side and too slow towards the normal side so that corrective saccades are needed for tracking the target (figs 3B, 4D). Visual suppression of the vestibulo-ocular reflex (VOR-supp, fig. 3D) is mainly impaired for rotation to the normal side when slow phases of VOR are directed to the side of the lesion (ipsilateral). The patient not only has difficulty in suppressing the vestibular response but also in keeping his eyes in midgaze position on the target due to their tendency to deviate to the side of the lesion (oblique arrow in fig. 3D). This tendency strongly breaks through when there is an additional vestibular drive towards the lesion side. On extinction of the fixation light (downward arrow in fig. 3D) while the patient is rotated in darkness, the eyes move within seconds towards the side of the lesion even against the oppositely directed vestibular drive. This interaction of spontaneous drift in midgaze position and slow eye movements explains the finding that the slow eye movements directed to the lesion side are even faster during suppression of the VOR than during

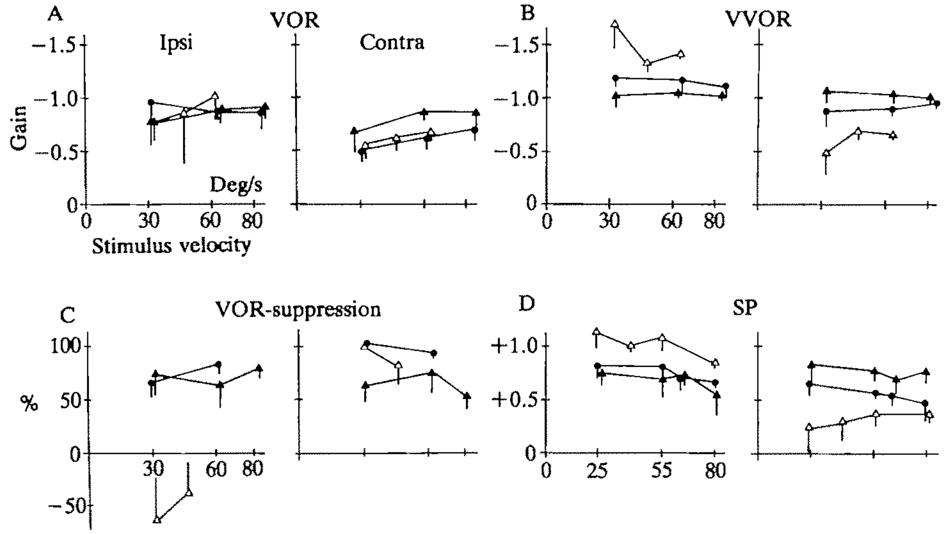


FIG. 4. Gain values with 1 SD in *Case 4* during VOR (A), VVOR (B), and SP (D), and percentage of VOR suppression (C) as a function of peak stimulus velocity (abscissa). In each panel values for slow eye movements to the lesion side (ipsi) are on the left and to the normal side (contra) on the right. Measurements are taken 5 days (open triangles, *see* fig. 3), 14 days (filled circles) and 6 months (filled triangles) after onset of symptoms. After 5 days average horizontal spontaneous drift in light in midgaze was 13 deg/s (range 9–18 deg/s) and the eyes deviated in darkness on average 25.5° (SD 8.3°) within 2.4±1.0 s (SD) towards the lesion side. After 14 days average drift velocity had decreased to 2 deg/s (range 0–5 deg/s) and the eyes deviated on average 19±7.5° within 4.5±2.8 s. After 6 months there was no horizontal spontaneous drift in light, but in darkness the eyes still moved towards the side of the lesion (fig. 2D).

VOR alone (fig. 4C). During sinusoidal rotation in front of a space-stationary target on which the patient fixates (VVOR, fig. 3C) the slow eye movements to the side of the lesion are too fast and those to the normal side too slow (fig. 4B). Corrective back-up and catch-up saccades against or in the direction of relative target movements are needed to keep the eyes on the target (fig. 3C). Note that in fig. 4A,B the gain of VOR (recorded on the fifth day) is only half of that of VVOR (which is well above 1.0) for slow phases to the side of the lesion (ipsilateral), because in darkness during VOR the eyes are deviated to the side of the lesion where spontaneous drift is absent (fig. 3D), whereas in light during VVOR the eyes are forced to pass through the midgaze position where spontaneous drift was on average 13 deg/s (fig. 3C). When Case 4 was retested 9 days later (14 days after onset of symptoms), the directional asymmetries of the slow eye movements were much less pronounced as spontaneous drift was minimal (fig. 4). During VOR suppression the slow eye movements to the lesion side were no longer faster than those during VOR alone.

These observations suggest that the spontaneous drift to the lesion side contributes considerably to the abnormalities and the directional preponderance of slow eye movements during visual-vestibular stimulation. This is further suggested by the eye position dependency of both spontaneous drift and slow eye movement velocities (fig. 5). Smooth eye movements away from the side of the lesion (in fig. 5A the lesion in

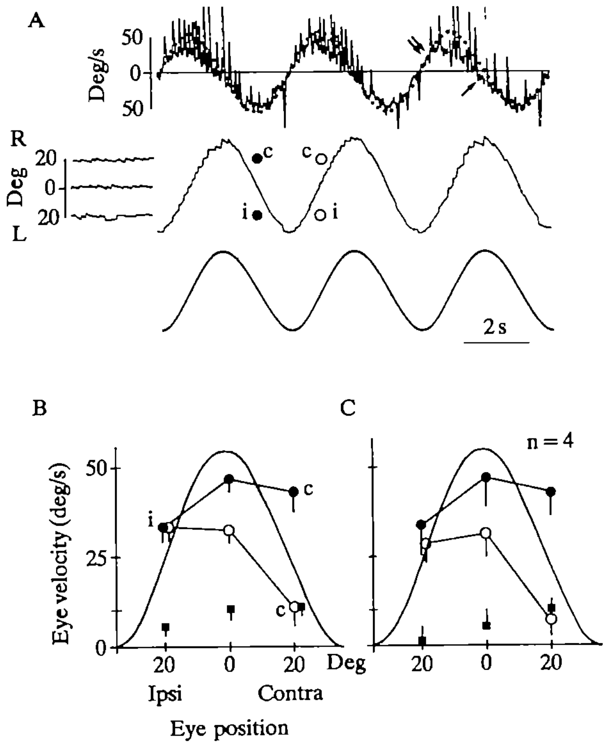


FIG. 5. A, horizontal eye movements in *Case 9* with a left-side lesion in response to a stationary (in midgaze position and 20° right (R) and left (L)) and to a sinusoidally moving fixation light (4 s ±35°). First line velocity of the eyes (sharp deflection corresponds to a saccade) and of the target (superimposed pointed line). Second and third line eye and target position, respectively. B,C, average values (1 SD) of eye velocity in *Case 9* (B) and in *Cases 3,4,5,9* (C) in response to the sinusoidally moving target light (4 s ±35°, peak velocity in midgaze position 55 deg/s) at different eye positions (abscissa) in midgaze (0°) and 20° ipsilateral (i) and contralateral (c). Filled circles are values for movements to the lesion side (*see* A), and open circles are the corresponding values for tracking movements to the normal side. Filled squares indicate velocities of spontaneous drift during fixation of the stationary target. The instantaneous velocity of the target is superimposed. Further explanation is given in the text.

Case 9 is on the left side, an upward deflection corresponds to a movement away from the side of the lesion) are for identical relative target velocities faster in ipsilateral than contralateral gaze positions. Smooth eye velocities correspond to stimulus velocity in ipsilateral gaze positions (double arrow in first line in A; ●^{i}, ○^{i} in B,C) but are too slow (○^{c}) or too fast (●^{c}) in contralateral gaze positions where spontaneous drift (■) is most prominent. In contralateral gaze positions, smooth eye movements reverse in direction before the target light starts to move away from the normal towards the side of the lesion (arrow in first line of A). Consequently, smooth eye movements are faster than target movements (●^{c}).

For the quantitative evaluation of their interaction the amount of the spontaneous drift cannot simply be subtracted from the slow eye movement velocity. Fig. 6 demonstrates

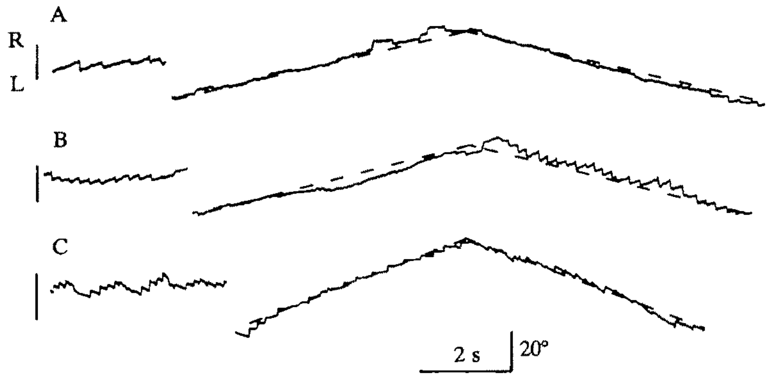


FIG. 6. Eye movements in the horizontal plane of 3 patients (*Case 5* in A, *4* in B, *9* in C) in response to the fixation light which is stationary in midgaze position (*left*) or which moves from 20° left to 20° right and back through the midgaze position. Target velocity is between 6 and 8 deg/s and approximates that of the spontaneous drift. Target (dashed line) and eye position traces are superimposed.

this point for 3 patients with spontaneous drift of comparable magnitude while fixating in midgaze position (left side). Case 5 (A) was able to track the target smoothly to both directions at a velocity of 7 deg/s which corresponded to that of his spontaneous drift. Case 4 (B) was, however, unable even to reverse the direction of his spontaneous drift for similarly slow target movements towards the normal side, whereas following eye movements in Case 9 (C) were respectively too slow and too fast for target movements towards the normal and lesioned sides.

In summary, in patients with the lateral medullary syndrome the spontaneous drift towards the side of the lesion that is dependent on eye position contributed considerably to the abnormalities of slow eye movements. Their directional preponderance was most prominent in the contralateral hemifield where drift velocity was strongest. It was, however, difficult to evaluate quantitatively the amount of this contribution. To answer our second question, namely that of a deficit in smooth pursuit movements themselves, we analysed oculomotor performance during visual-vestibular interaction at a time during the acute and chronic stage of the illness when spontaneous drift was absent or minimal. In the following, the slow eye movement abnormalities will be discussed separately for the acute (up to 3 wks after onset of symptoms) and chronic stages.

Slow eye movements in the acute stage (up to 3 wks)

We will present the measurements in these 6 patients first in whom a single focal area of pathological signal intensity was visualized in the (dorso)lateral medulla but not in the cerebellum (Cases 1–6). Following this presentation we will discuss the results in Cases 8–12 with cerebellar infarction. The gain-velocity characteristics for a velocity of 55 deg/s (SP), 63 deg/s (VOR; VVOR) and 80 deg/s (OKN) obtained in the two patient groups are compared in Table 2.

Cases 1–6 with lateral medullary infarction

Spontaneous drift. At the time of analysis Cases 1, 4 and 5 still had some spontaneous drift in midgaze position to the side of the lesion with a mean velocity of the horizontal component of 5, 2 and 7 deg/s, respectively.

Vestibulo-ocular reflex (VOR). Gain was asymmetric in all patients, being higher for slow movements directed to the side of the lesion (fig. 7A, Table 2). The asymmetry

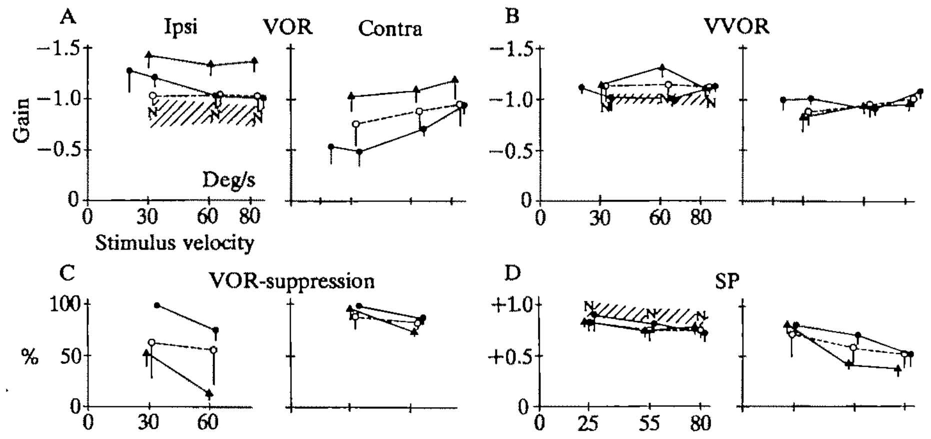


FIG. 7. Gain values during VOR (A), VVOR (B) and SP (D) and percentages of VOR suppression (C) for patients with medullary infarction in the acute stage (open circles = average values with 1 SD for *Cases 1–6*; filled circles and triangles = values for *Cases 2* and *3*, respectively). Same display as in fig. 4. Normative values with average (N) and ± 1 SD (dashed area) are given in A, B and D.

TABLE 2. AVERAGE GAIN VALUES WITH RANGES OF SP, OKN, VOR, VVOR, AND PERCENTAGE OF VOR SUPPRESSION FOR SLOW EYE MOVEMENTS TO THE LESION (IPSI) AND NORMAL (CONTRA) SIDE IN THE ACUTE STAGE

	Cases 1–6		*Cases 10–12*		*Normals*
	Ipsi	*Contra*	*Ipsi*	*Contra*	*(n = 10)*
SP (4 s±35°; 55 deg/s)	0.77 (0.60–0.87)	0.59 (0.41–0.79)	0.71 (0.61–0.77)	0.76 (0.68–0.82)	0.90 (0.84–0.97)
OKN (80 deg/s)	0.60 (0.41–0.71)	0.44 (0.30–0.68)	0.52 (0.43–0.66)	0.51 (0.39–0.64)	0.85 (0.80–0.92)
VOR (4 s±40°; 63 deg/s)	1.04 (0.88–1.34)	0.85 (0.63–1.09)	0.88 (0.86–0.90)	0.97 (0.92–1.00)	0.87 (0.71–0.97)
VVOR (63 deg/s)	1.15 (1.00–1.31)	0.95 (0.74–1.07)	0.99 (0.97–1.02)	1.00 (0.98–1.02)	1.02 (0.90–1.12)
VOR suppression (63 deg/s)	56% (13–95)	84% (75–89)	83% (76–87)	75% (61–85)	>95%

was most conspicuous in Case 2. In Case 3, VOR-gain was above 1.0 for stimulation in both directions. On average, VOR gain with slow phases to the side of the lesion was slightly higher than in control subjects.

Visuovestibulo-ocular reflex (VVOR). The responses were still asymmetric (fig. 7B; Table 2). In Cases 2–5 the slow tracking movements to the ipsilateral side (usually only at lower stimulus velocities) were too fast and interrupted by corrective back-up saccades directed against relative target movement.

VOR suppression. Visual suppression of VOR was also asymmetric and (for higher stimulus velocities) mostly below normal limits. Suppression was less for rotation to the contralateral side (i.e., for ipsilaterally directed slow eye movements) (fig. 7C; Table 2). Impaired visual suppression paralleled the deficits in smooth pursuit velocities with the appropriate directionality (Table 2).

Smooth pursuit. Gain was asymmetric in all patients except Case 5, being less and below normal for movements to the contralateral, undamaged side (fig. 7D; Table 2). The deficit was larger at higher stimulus velocities. With a low gain many corrective catch-up saccades were needed for tracking the target. For ipsilateral movements SP gain was on average slightly below normal. In Case 5 gain was normal for lower stimulus velocities and symmetrically reduced for stimulus velocities above 40 deg/s.

OKN. In all 5 patients tested, OKN slow phase velocities were affected similarly to SP velocities. For a stimulus velocity of 40 deg/s gain was on average 0.80 (range 0.62–0.94) for ipsilateral stimulation and 0.64 (range 0.45–0.77) for contralateral stimulation. For a stimulus velocity of 80 deg/s gain was on average 0.60 (range 0.41–0.71) for ipsilateral slow phases and 0.44 (range 0.30–0.68) for contralateral slow phases (Table 2).

In summary, in patients with infarction in the (dorso)lateral medulla and with no cerebellar involvement, vestibular and visual slow eye movements could still be asymmetric when spontaneous drift was minimal or absent. Smooth pursuit was strongly impaired for movements to the normal side, but also for movements to the side of the lesion. This corresponded to a marked deficit of visual suppression of the VOR for stimulation to the normal side. We conclude that the asymmetries and deficiencies in visually controlled slow eye movements are not solely explained by the presence of spontaneous drift. Pathways are interrupted in the lateral medulla which mediate visual and/or motor signals for the control of slow eye movements.

Cases 8–12 with cerebellar infarction

Case 8 (fig. 1D–F) who could only be examined at the bedside and Case 9 (Table 1; figs 2C, 5A,B, 6C) also had medullary infarction. Their oculomotor disturbances with spontaneous drift, saccadic lateropulsion and a preponderance of slow eye movements to the side of the lesion were indistinguishable from those of patients with infarction in the lateral medulla only. After resolution of the spontaneous drift in Case 9, smooth eye movements during SP and OKN were impaired for stimulation in both directions, as in Case 5, whereas VOR and VVOR gains were unremarkable.

Cases 10–12 with cerebellar infarction comparable in localization and size to that of Case 8 but with no medullary involvement had asymmetric VOR gains, being higher for slow phases to the normal side (Table 2). VVOR gains were normal and symmetric. Smooth pursuit, OKN and VOR suppression were impaired bilaterally. SP gain ranged between 0.88 at 25 deg/s, and 0.57 at 80 deg/s, being slightly worse for ipsilateral stimulation (Table 2). OKN gain was symmetrically reduced and ranged between 0.73 at 40 deg/s and 0.51 at 80 deg/s.

In summary, Cases 8 and 9 showed severe oculomotor disturbances, comparable to those of patients with infarction confined to the lateral medulla. Cases 10–12 with no clinical and radiological signs of medullary infarction also had bilaterally deficient visually elicited slow eye movements. In contrast to Wallenberg's patients, abnormalities of SP, VOR and VOR suppression tended to be more prominent for stimulus movements to the ipsilateral side.

Slow eye movements in the chronic state (3 to 20 months)

We will again discuss first the oculomotor findings in these patients with infarction in the lateral medulla but with no cerebellar involvement. The gain-velocity characteristics at 55 deg/s (SP), 63 deg/s (VOR, VVOR) and 80 deg/s (OKN) obtained in the two patient groups are compared in Table 3.

TABLE 3. AVERAGE GAIN VALUES WITH RANGES OF SP, OKN, VOR, VVOR, AND PERCENTAGE OF VOR SUPPRESSION IN THE CHRONIC STAGE

	Cases 2–7		*Cases 10–12*		
	Ipsi	*Contra*	*Ipsi*	*Contra*	*Normals (n = 10)*
SP	0.80	0.67	0.86	0.86	0.90
(55 deg/s)	(0.67–0.88)	(0.50–0.82)	(0.77–0.91)	(0.76–0.92)	(0.84–0.97)
OKN	0.57	0.59*	0.79	0.76	0.85
(80 deg/s)	(0.50–0.64)	(0.48–0.69)	(0.72–0.90)	(0.74–0.77)	(0.80–0.92)
VOR	0.94	0.90	0.78	0.78	0.87
(63 deg/s)	(0.88–1.00)	(0.78–0.99)	(0.70–0.83)	(0.74–0.86)	(0.71–0.97)
VVOR	1.00	0.99	1.01	1.04	1.02
(63 deg/s)	(0.93–1.03)	(0.92–1.07)	(0.99–1.03)	(1.03–1.05)	(0.90–1.12)
VOR suppression	80%	78%	95%	91%	>95%
(63 deg/s)	(63–94)	(73–92)	(90–100)	(90–100)	

*Tested in Cases 4,5,7 only.

Cases 2–7 with lateral medullary infarction

VOR and VVOR. Average gains (○ fig. 8A,B; Table 3) were unremarkable except for a tendency of the VOR gain to be relatively high.

VOR suppression. Visual suppression of VOR was deficient bilaterally at higher stimulus velocities (fig. 8C; Table 3).

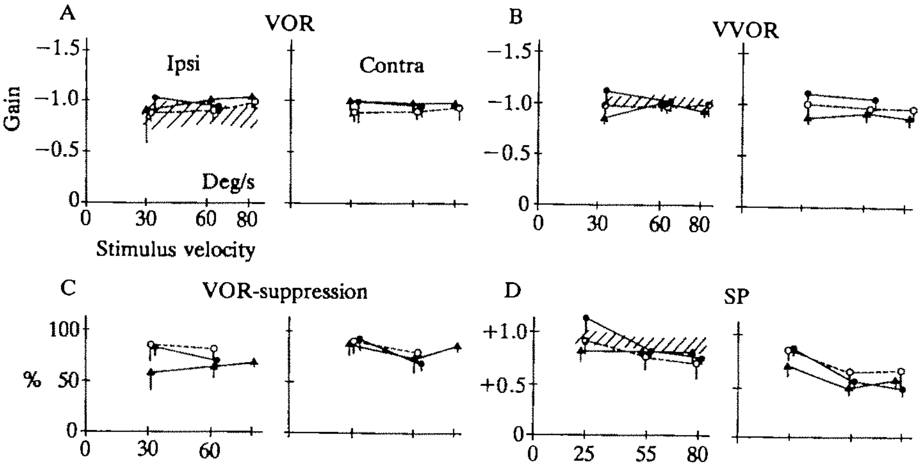


FIG. 8. Same display as in fig. 7. Values for patients with medullary infarction in the chronic stage (open circles = average values for *Cases 2–7*; filled circles and triangles = values for *Cases 2* and *3*, respectively).

Smooth pursuit. In 5 patients SP was impaired bilaterally at higher velocities but more so for stimulation either to the normal side (3 patients; fig. 8D) or to the side of the lesion (Cases 4, 5; fig. 4D). In Case 6 SP gain was within normal limits.

OKN. Optokinetic responses were tested in 3 patients (Cases 4,5,7). Gain averaged 0.81 (range 0.78–0.84) for ipsilateral and 0.69 (range 0.58–0.77) for contralateral stimulation at 40 deg/s; and 0.57 (range 0.50–0.64) for ipsilateral and 0.59 (range 0.48–0.69) for contralateral stimulation at 80 deg/s.

In summary, eye movement performances improve with time. In most patients with lateral medullary infarction, however, deficits in SP and VOR suppression persisted for months in the absence of spontaneous drift, supporting the conclusion that pathways are interrupted in the lateral medulla carrying information which is crucial for the visual control of slow eye movements. Although the deficits were on average bilateral, some directional preponderance was usually present.

Cases 8–12 with cerebellar infarction

Case 8 had the worst outcome of all patients for both oculomotor and postural control. Visual and vestibular slow eye movements were symmetrically abnormal and the amount of impairment depended on stimulus parameters. He was the only patient in whom VOR and VVOR gain was consistently above 1.0 at all or at higher stimulus velocities, respectively (■ fig. 9A,B). VOR suppression and SP were equally impaired for stimulation in both directions (■ fig. 9C,D). OKN was also impaired bilaterally with a gain of 0.43 at 40 deg/s and 0.22 at 80 deg/s. Case 9 had deficient OKN, SP and VOR suppression for stimulation to both sides, but deficits were more marked for ipsilateral stimulation.

In Cases 10–12 oculomotor performance was improved. VOR and VVOR gain values

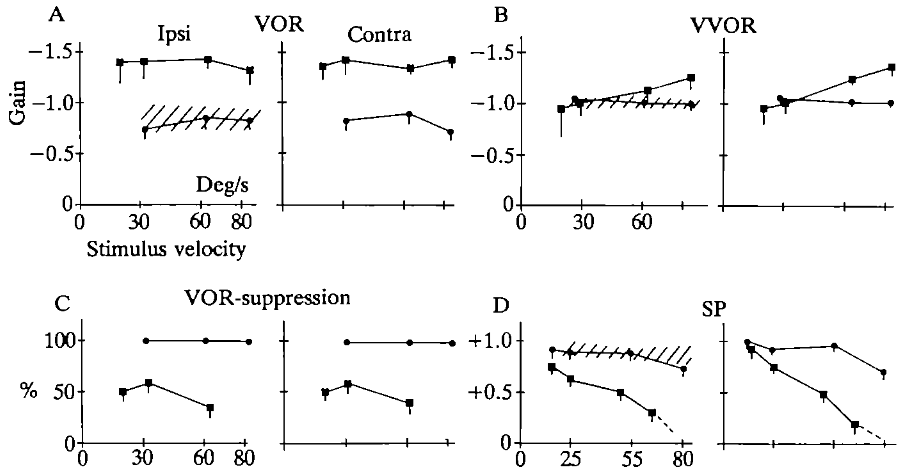


FIG. 9. Same display as in fig. 8. Values for *Case 8* (filled squares) with medullary and cerebellar infarction, and for *Case 10* (filled circles) with cerebellar infarction in the chronic stage.

were within normal limits. SP was normal in Case 12, deficient in Case 10 at the highest stimulus velocity (fig. 9D ●) and in Case 11 symmetrically at all velocities. SP gain values for the 3 patients ranged between 0.91 at 25 deg/s, and 0.77 at 80 deg/s. OKN gain was slightly and symmetrically reduced and ranged between 0.87 at 40 deg/s, and 0.77 at 80 deg/s. Mean gain values of VOR, VVOR, and SP and percentage of VOR suppression in Case 10 are displayed in fig. 9′(●).

In summary, Cases 10–12 with a cerebellar infarction had no or minimal, persistent slow eye movement abnormalities. In contrast, Case 8 with a chronic cerebellar infarction similar in extent to that in Case 10 but with an additional large medullary lesion, had severely and symmetrically disturbed slow eye movement performance.

DISCUSSION

The oculomotor signs which occur with the *acute* lateral medullary syndrome have been described mostly in single case studies (Moberg *et al.*, 1962; Daroff *et al.*, 1968; Kommerell and Hoyt, 1973; Hamann, 1979; Kirkham *et al.*, 1981; Cambier *et al.*, 1982; Benoit *et al.*, 1987), but seldom for larger groups of patients (Hagström *et al.*, 1962; Baloh *et al.*, 1981; Estañol and Lopez-Rios, 1982). A few studies only analysed in some detail the oculomotor performance during visual-vestibular interaction. Baloh and coworkers (Meyer *et al.*, 1980; Baloh *et al.*, 1981) described 6 patients who had slow eye movement abnormalities similar to, albeit more dramatic, than those observed in our patients. The prominent features were spontaneous nystagmus in light with its horizontal component beating to the intact side, a tendency of the eyes to deviate tonically to the side of the lesion, and saccadic smooth pursuit to the normal side and impaired visual suppression of VOR with rotation to the undamaged side. Directionality of impaired

SP and VOR suppression was preserved even in these 3 patients in whom spontaneous nystagmus changed its direction in darkness, a feature not observed in our patients. The 9 patients reported by Estañol and Lopez-Rios (1982) did not show the same consistent uniformity in the laterality of their slow eye movement abnormalities. In these two studies the contribution of the spontaneous nystagmus to the eye tracking abnormalities and asymmetries was not further assessed. Also, a clinicoanatomical correlation was not possible by CT imaging. As we observed 3 Wallenberg's patients with a verified lesion in the dorsolateral medulla (*see* Patients and Methods) who had normal oculomotor performance, we wondered if it was the spontaneous drift which caused most of the eye tracking abnormalities. We also wondered whether the oculomotor disturbances were different in patients with and without cerebellar infarction as revealed by MRI.

Three conclusions drawn from our results are of importance and will be discussed. (1) In most patients with the symptoms and clinical signs of the lateral medullary syndrome the cerebellum is structurally (but probably not functionally) intact as demonstrated by MRI (2). Spontaneous drift, interpreted as a manifestation of the pulling force or 'ocular lateropulsion' which deviates the eyes to the side of the lesion makes a considerable contribution to but does not wholly account for the directional preponderance and the abnormalities of slow eye movements during visual-vestibular interaction. (3) Spontaneous drift to the side of the lesion and 'ocular lateropulsion', as well as amplitude asymmetries of fast eye movements, are consequent on the disruption of structures and pathways in the lateral medulla as these oculomotor signs were not observed in patients with infarction in the cerebellar territory of the PICA alone. Furthermore, as slow and fast eye movements were deficient when spontaneous drift and tonic deviation had resolved and when the cerebellum was intact, the pathways interrupted in the lateral medulla mediate sensory and/or motor signals which are important for the visual control of eye movements by the cerebellum. An interesting alternative explanation is that, although the cerebellar cortex is structurally intact, the efficacy of Purkinje cells is reduced due to the mere disruption of olivocerebellar pathways regardless of the signals conveyed.

Spontaneous drift and slow eye movement abnormalities

We assume that the spontaneous drift and the tonic deviation to the side of the lesion are manifestations of the same pulling force acting on both eyes. The nature and origin of this force or 'ocular lateropulsion' is unclear. Both the linear profile and the dependency on eye position of the velocity of the spontaneous drift has often been observed (Kommerell and Hoyt, 1973; Baloh *et al.*, 1981; Estañol and Lopez-Rios, 1982). The eye position dependency may be due to deficient gaze-holding mechanisms which integrate horizontal eye velocity to position command signals (Robinson *et al.*, 1984; Cannon and Robinson, 1987; Morrow and Sharpe, 1988). The linear profile of the drift velocity rather suggests a tone asymmetry or push-pull imbalance within the canal/otolithic-vestibular system. Cannon and Robinson (1987) demonstrated that a combination of both gaze-evoked nystagmus due to a leaky integrator and vestibular tone imbalance produces a drift which offsets the null position of the eyes where drift is zero, as in our patients. In 6 patients the values of the time-constant of the leaky eye position integrator would be between 2.5 and 4.5 s in darkness and 3.5 and 8 s in light, measured by the equation described by Robinson *et al.* (1984). In Cases 10–12 there was also some leakiness of the integrator in darkness. The time constant ranged in darkness between 5.5 and over 15 s; in light it was always above 15 s. 'Ocular lateropulsion' may therefore be consequent on the structural or functional disruption of pathways which are important for gaze holding mechanisms and the maintenance of tonic balance within the vestibular system. Why interference with these mechanisms also affects the saccadic system is unclear (Kommerell and Hoyt, 1973).

A measure of the strength of the pulling force is the velocity of the spontaneous drift and the time that it takes for the eyes to deviate towards the null position on the side of the lesion. Although the severity of slow and fast eye movement asymmetries roughly parallels the strength of the pulling force, eye movement performance may be deficient even when the pulling force is minimal or absent.

Patients with infarction limited either to the lateral medulla or to the cerebellum had bilaterally deficient SP, OKN and suppression of VOR. Some differences, besides the absence of 'ocular lateropulsion' to the side of the lesion in cerebellar patients, are noteworthy. SP performance was better in acute Wallenberg patients for ipsilateral and in cerebellar patients for contralateral movements. Gain differences (measured at a time when spontaneous drift was minimal or absent) between both sides ranged in Wallenberg's patients between 0.13 and 0.23 for stimulus velocities of 25 and 80 deg/s and 0.04 and 0.08, respectively, in cerebellar patients. In the chronic stage of Wallenberg syndrome, SP performance in individual patients was better either for ipsilateral or contralateral movements. The symmetric slow eye movement abnormalities and the consistently increased VOR gain in Case 8 who had the most extensive lesion are of interest. It is also tempting to ascribe most of the abnormalities to the lesion in the lateral medulla in this patient, because the 3 patients with comparable extensive cerebellar infarction but no medullary involvement did not show increased VOR gain and had no or much less severe SP and OKN gain deficits. Cases 8 and 10 will be important when considering pathophysiological and anatomical aspects of the lateral medullary syndrome.

MRI and anatomical aspects

Fisher *et al.* (1961) observed that 12 of 16 autopsied patients with the clinical diagnosis of Wallenberg's syndrome and with softening in the lateral medulla oblongata had no associated cerebellar involvement. The autopsied patient reported by Moberg *et al.* (1962) also had no cerebellar involvement. On the other hand, cerebellar infarction in the territory of the posterior inferior cerebellar artery (PICA) may not be accompanied by infarction in the lateral medulla (Duncan *et al.*, 1975). Thus our MRI findings agree well with these previous reports in that the cerebellum is often intact in patients with infarction in the dorsolateral medulla (Bogousslavsky *et al.*, 1986).

The PICA has the most complex and variable course of the three cerebellar arteries (Fisher *et al.*, 1961; Gillilan, 1964; Lister *et al.*, 1982). Its penetrating (intrinsic) branches supply the lateral sector of the medulla, and the circumferential (extrinsic) branches supply the inferior (suboccipital) cerebellar surface (including the nodulus and tonsil) up to the primary horizontal fissure. The flocculus is supplied by the anterior inferior cerebellar artery (AICA) but not by the PICA (Amarenco *et al.*, 1989; *see*, however, Lister *et al.*, 1982, and autopsied Case 1 of Duncan *et al.*, 1975). The major branches of the cerebellar arteries are highly anastomotic and connections are unpredictable (Lister *et al.*, 1982). This may be the reason why in vertebral artery or PICA occlusion often only the medullary penetrating branches, which are true end-arteries, are affected but not the cerebellar branches (Fisher *et al.*, 1961; Gillilan, 1964). From autopsy material it is obvious that the extent of infarction in the lateral medulla is variable; multiple small infarcts are also possible. In cross-sections the most common zone of infarction embraces a wedge of the lateral medulla dorsal to the inferior olive (IO). This zone most regularly involves crossed olivocerebellar fibres at the entrance to and in the inferior cerebellar peduncle or restiform body itself (Fisher *et al.*, 1961; Nieuwenhuys *et al.*, 1978; Voogd and Bigaré, 1980). In the rostrocaudal direction the infarct is most commonly at the level of the middle one-third of the inferior olive (Fisher *et al.*, 1961). The lesion seldom extends dorsally to involve the caudal vestibular nuclear complex or ventrally to involve the IO nucleus (Fisher *et al.*, 1961). Infarction of the lateral (but not of the dorsal) territory of the medulla is very rarely accompanied by cerebellar infarction (Amarenco *et al.*, 1989).

Several nuclei in the medulla oblongata, known to be important in the regulation of slow eye movements, project either directly as mossy fibres and/or indirectly via the IO as climbing fibres to the cerebellum. The climbing fibre pathway travels in the inferior peduncle and is completely crossed. Neurons in the caudal vestibular nuclear complex and in the prepositus hypoglossi nucleus send axons directly to the (para)flocculus via the inferior cerebellar peduncle, but bilaterally (Brodal and Brodal, 1985; Langer *et al.*, 1985*a*). It is not known precisely where these mossy fibres join the inferior peduncle. The lateral reticular nucleus is another relay nucleus within a vestibulo-reticulo-cerebellar pathway (Precht *et al.*, 1977). It sends a few fibres to the (para)flocculus (Langer *et al.*, 1985*a*), but nothing is known about its role in oculomotor control. It is generally assumed that visual mossy fibre inputs to the (vestibulo) cerebellum originate in the pontine nuclei and the nucleus reticularis tegmenti pontis (for summary, *see* Waespe and Henn, 1987). These mossy fibres reach the cerebellum via the middle cerebellar peduncle (brachium pontis) which is not involved in Wallenberg's syndrome. The axons of (para)floccular Purkinje cells to their target cells in the rostral vestibular nuclear complex pass more anteriorly and dorsally near the dentate nucleus (Langer *et al.*, 1985*b*). They are not interrupted by lateral medullary lesions.

MRI readily visualizes the infarcted areas in the lateral medulla and the cerebellum; but it is difficult to be certain of their precise extent. In none of our patients was infarction bilateral. Considerations of pathophysiological aspects of oculomotor signs in Wallenberg's lateral medullary syndrome are still speculative. However, in conformity with the findings in autopsy material, infarcted areas in the medulla most regularly involve its lateral aspect where olivocerebellar fibres join the inferior peduncle (Table 1). There are a few animal studies, mostly in lower species, which lend support to the idea proposed by Hoyt and Frisén (1975) that interruption of olivocerebellar fibres contribute to some of the oculomotor abnormalities.

Pathophysiological and functional considerations

There is ample evidence that the vestibulocerebellum, especially its floccular part, and probably also the adjacent ventral and dorsal paraflocculus, have a major role in the visual control of slow eye movements (Lisberger and Fuchs, 1978; Miles *et al.*, 1980; Waespe *et al.*, 1983, 1985*a*; Noda and Mikami, 1986). The nodulus and ventral uvula seem to be of minor importance (Waespe *et al.*), 1985*b*). In the monkey it is not clear if what is considered to be folia 5–10 of the flocculus might not actually belong to the ventral paraflocculus. The tonsil in man corresponds to the ventral paraflocculus. Since in many Wallenberg patients the cerebellar cortical structures are anatomically intact as demonstrated by MRI, interruption of fibres passing in the lateral medulla to the vestibulocerebellum or its floccular part may contribute to the abnormalities of eye movement. It is not yet clear if the control functions exerted by the vestibulocerebellum on slow eye movements are attributable to mossy fibre or climbing fibre inputs, or to a combination of both. Mossy fibres convey a variety of signals to the vestibulocerebellum. Activity can be related to several eye movement parameters and to vestibular and visual motion information. We are unfortunately ignorant about the role of specific mossy fibre input channels in the information processing of the vestibulocerebellum. The effects of selective interruption of mossy fibres travelling in the inferior peduncle and originating in medullary nuclei are also not known. Olivo(para)floccular climbing fibres may participate in the immediate control of slow eye movements by conveying directionally selective visual movement information (Waespe *et al.*, 1981; Stone and Lisberger, 1986; Graf *et al.*, 1988). There is the hypothesis that IO neurons relay signals about image motion or retinal slip to the cerebellum for modulating slow eye movements but also for improving the time constant of the eye position integrator (Robinson, 1989). After selective IO lesions oculomotor deficits in the rat are similar to those after surgical flocculectomy (Hess *et al.*, 1988). They are remarkably similar to those in (para)flocculectomized monkeys (Zee *et al.*, 1981; Waespe *et al.*, 1983). In both species gaze-holding failure occurs, namely the ability to maintain eccentric gaze is impaired, and the short-time constant mechanisms of OKN, believed to be identical to mechanisms which produce SP eye movements in primates (Robinson, 1981; Waespe *et al.*, 1985*a*), are impaired. After destruction or reversible inactivation of the IO or of climbing fibres to the flocculus spontaneous simple spike firing rate of Purkinje cells increases by about 100%, and then slowly returns to normal over 2–4 wks (Benedetti *et al.*, 1983, 1984; Demer *et al.*, 1985). As a consequence, vestibular target cells are silenced by this tonic increase in the inhibitory action of Purkinje cells (Benedetti *et al.*, 1983). The transient increase in simple spike activity in these cells after *unilateral* IO deafferentation thus induces a tonic imbalance between the two vestibular nuclear complexes. The tonic activity of the vestibular nuclear complex contralateral to the inferior olivary lesion is decreased relative to that on the opposite side and this imbalance in activity induces a drift of the eyes to the side contralateral to the IO lesion (Barmack and Simpson, 1980; Demer and Robinson, 1982). This conjugate drift often has a down component. The spontaneous drift (lasting 1–3 wks) in Wallenberg's syndrome, with its horizontal slow component to the side of the lesion and with often a downward slow component, may be explained by the transient tonic shift in spontaneous firing rate of Purkinje cells and their vestibular target cells ipsilateral to the lesion. In order to have the correct directionality of the drift, it has to be remembered that in Wallenberg's syndrome the olivocerebellar fibres from the contralateral IO are interrupted after they have already crossed in the medulla. Unilateral lesions of the flocculus and paraflocculus with destruction of Purkinje cells induce a conjugate drift of the eyes to the side contralateral to the lesion (Waespe *et al.*, 1983; Barmack and Pettorossi, 1985), that is, to the side ipsilateral to the IO from which the vestibulocerebellum receives its climbing fibre input. Reversible inactivation of the decussating fibres from both IOs with lidocaine increased VOR gain to an average value of 1.5 (Demer and Robinson, 1982), values similar to those in Cases 3 (acute stage) and 8 (chronic stage) in the present study. This gain could be reduced in light by vision, but VVOR gain was still considerably above 1.0. The permanently deficient visual control of tracking eye movements may be related to interruption of olivo(para)floccular pathways which transmit visual motion information. Stones and Lisberger (1986) suggested that the visually related climbing fibre input to the monkey (para)flocculus improves smooth pursuit performance by detecting small errors during inaccurate tracking. An interesting alternative possibility is a more unspecific effect as *chronic* IO deafferentation results in a reduced efficacy of the inhibitory action of Purkinje cells, thus decoupling vestibular target cells functionally, yet not anatomically, from the cerebellar cortical output (Karachot *et al.*, 1987). This could explain why in some patients the SP performance in the chronic stage is more strongly impaired for ipsilateral movements, as after cerebellar cortical lesions. Thus even if cerebellar cortical circuits received normal mossy fibre input signals, inhibitory Purkinje cell action on their target cells would be less effective due to the mere disruption of climbing fibre input activity regardless of the specific information carried by the damaged climbing fibres. Case 8 had the strongest permanent deficits in visually controlled slow eye movements. These deficits were symmetric despite a unilateral lesion, and the VOR was hyperactive. A VOR gain above unity in our opinion excludes the possibility that damage to the caudal vestibular nuclei is responsible for the abnormalities. MRI suggested that the extensive medullary lesion interrupted olivocerebellar pathways bilaterally. Infarction of the flocculus cannot be excluded but control MRI did not suggest atrophy of the floccular area. Recently, Thurston *et al.* (1987) attributed a hyperactive VOR and deficient SP in a patient with cerebellar degeneration to olivocerebellar dysfunction.

In summary, Wallenberg's syndrome can present a wide array of oculomotor deficits. MRI and necropsy studies suggest that in many patients infarction is limited to the lateral medulla and that the cerebellum is structurally intact. There is no convincing proof as to the precise mechanism of the transient and persistent slow eye movement abnormalities.

The main deficits could be explained, based on a few animal experiments, by interruption of olivocerebellar circuitries in the lateral medulla. The transient drift to the side of the lesion that is dependent on eye position would be related to a general increase in spontaneous simple spike activity of Purkinje cells due to climbing fibre disruption, whereas the deficits in gaze holding mechanisms and in SP, OKN and VOR suppression would be related more to a lack of climbing fibre input to the (para)flocculus which transmits specific information about image motion.

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BOOK REVIEWS

Merritt's Textbook of Neurology. Eighth edition. Edited by Lewis P. Rowland. 1989. Pp. 964. Beckenham, Kent: Lea and Febiger. Price £49.50.

This eighth edition of Merritt's Textbook is published 34 years after the first edition, written by Houston Merritt himself, appeared in 1955. An edition on average once every 4 years or so with an additional total of 15 reprintings is ample evidence of the popularity of this text, and is well justified. It is of course a great deal longer than the earliest editions and provides a comprehensive neurological textbook in one volume. Styles in a book with 75 contributors must of course vary but the Editor, Dr Lewis P. Rowland, has managed to achieve a remarkable degree of uniformity in the book and it should be noted that his personal contribution extends to 25 of the total 162 chapters. None of the sections is too long to be read from beginning to end but the book is wide-ranging enough in its scope to be a very useful work of reference, and anyone who consults it will be struck by the up-to-date lists of references (conveniently grouped into subsections where necessary) at the end of each chapter. Imaging of one sort or another has become a very important part of the practice of neurology and adequate consideration of techniques and their usefulness is an important feature of any modern text. The subject is very well covered here and the reproduction of CT and magnetic resonance images are excellent.

There are of course points which any reviewer must raise for the authors to consider in future editions. The use of the words 'objective tinnitus' to describe a bruit which the patient can hear seems clumsy and unnecessary. I do not think that it is most neurologists' experience that headache is a common feature of pituitary adenoma (except perhaps in acromegaly) and optic atrophy and disc pallor are infrequent except in the last stages of chiasmal compression. It may be invidious to select particular chapters for special commendation but the reviewer was impressed with the chapters on vascular disease, demyelinating disorders and epilepsy. The book is well produced and good value.

C. J. EARL

Neurology: A Concise Clinical Text. By Michael Swash and Martin S. Schwartz. 1989. Pp. 400. London: Bailliere Tindall. Price £14.95.

Students often ask their teachers to recommend a text book. Just as there are horses for courses, there are tomes for drones, books for looks, texts for the perplexed, editions for erudition—and no doubt readers will add other varieties. For the undergraduate medical student and young doctor there are several excellent books of clinical neurology. Here is another. In their intriguing preface, the authors indicate some of the dilemmas they had to resolve. To what extent should such a book be traditional in format, reflect current influences, research and the particular interests of the writers? Should it be disease or problem orientated? The list is endless: should it be an introduction or a companion? How dogmatic and how discursive and analytical? To what extent should it cover basic sciences, encroach upon paediatrics, geriatrics or other medical specialties? This is an important decision for the punch-drunk student as he staggers from one module to another in an increasingly congested timetable.

The authors are resolute in intent. They firmly leave neurobiology to the neuroscientists, delegate clinical method to bedside teaching and concern themselves primarily with neurological symptoms and syndromes and with their management and treatment. As a consequence, they have produced an admirably balanced and relevant account. An unusual and welcome introductory chapter deals with the history of neurology. Of necessity brief, it extends from Aristotle to Hounsfield and will stimulate and entertain the more intelligent student and provide comforting reassurance that in the curriculum there is at least one subject in which consideration is still given to scholarship, philosophy and cultural awareness. Thereafter, chapter topics cover common symptoms—fits, faints, blackouts, headaches and facial pain, dizziness and vertigo—then specific diseases and syndromes supplemented by sections on pain and paediatric neurological problems. The text is generously illustrated with line drawings and well selected examples of modern neuro-imaging. The content is comprehensive and the authors clearly agree with Ben Johnson's definition of the concise style, that 'which expresseth not enough but leaves somewhat to understand'. Students and their teachers will welcome this fine textbook.

GERALD STERN

Myotonic Dystrophy. Second edition. By Peter S. Harper. 1989. Pp. 384. London: W. B. Saunders. Price £40.00.

It is 10 years since the publication of the previous edition of this monograph. Now, most chapters are expanded and there is an additional section on gene mapping and molecular genetics. The book undoubtedly gives a most comprehensive account of myotonic dystrophy and is excellent in the cover of its clinical and metabolic aspects. Clinical information that has accrued since 1979 includes enumeration of the obstetric risks of myotonic dystrophy in females, CAT studies of affected infants, and follow-up of neonatal and childhood-onset myotonic dystrophy, an account of a large consanguineous family from north-west Quebec, further descriptions of the Labrador family in which the clinical picture is a little unusual, and, most important, mapping of the gene for myotonic dystrophy to 19q, close to the locus for apolipoprotein C2. This latter discovery has meant that individuals at risk for inheriting the myotonic dystrophy gene can be offered carrier detection and prenatal diagnosis with 98% accuracy. It is probable that the gene will be identified and sequenced by the third edition of this book and it can then be determined whether there are several mutant alleles at the same locus and if so, whether they account for some of the clinical variation of myotonic dystrophy.

It is intriguing that there are still unanswered questions about the mode of inheritance of myotonic dystrophy. Professor Harper refers to the work of Höweler *et al.* (recently published in *Brain*) and concludes that his Dutch pedigrees, which are linked by three or four generations of apparently asymptomatic (but deceased) individuals, provide evidence for real, not imaginary, anticipation. Does anticipation indeed exist, to explain why gene carriers of one generation develop muscle symptoms while ancestral relatives have cataracts only? If so, what can be the mechanism? Do other researchers agree that the asymptomatic gene-carrying parent is usually the father, which raises the possibility of genomic imprinting? Harper briefly refers to Penrose on the question of anticipation, but does not remind his readers of Penrose's suggestion (*Annals of Eugenics,* 1947–1949) that allelic genes may modify the manifestation of myotonic dystrophy. On this theory one would expect little correlation in severity between affected parent and affected child, but 0.5 correlation between affected sib and affected sib. A long-term follow-up of the sibs of adult-onset patients might help to resolve the issue. In any case Penrose's theory could not explain the temporary severe illness that affects gene-carrying babies of affected women. It is interesting that recent work has shown that the muscle development of new-born rats may be affected by a humoral factor. Whatever the cause of neonatal myotonic dystrophy, Professor Harper has usefully shown that gene-carrying sibs are almost always affected in infancy or childhood.

It is good that Professor Harper not only reports but also inquires and stimulates. He writes simply and clearly although in this edition some verbosity has appeared. His book remains an invaluable reference source for neurologists, endocrinologists, anaesthetists, obstetricians and others who come across myotonic dystrophy in one of its manifold aspects, and who have to manage or advise patients. Many congratulations on this excellent second edition.

SARAH BUNDEY

Handbook of Neurological Investigations in Children. By John B. P. Stephenson and Mary D. King. 1989. Pp. 244. London: Butterworth. Price £25.

There is a tradition in British medicine of selectivity in investigation, avoiding the 'blunderbus' or 'fishing expedition' approach sometimes favoured elsewhere. This is especially desirable in the paediatric field where many factors combine to make exhaustive investigations inappropriate. In the special area of child neurology the choice of investigation may be particularly difficult, above all for those, whether general paediatricians or general neurologists, whose main experience lies elsewhere. Though child neurology is now well served with books reviewing the clinical diagnostic approach, a substantial work devoted to neurological investigations in children has been lacking until now. This requires a wide experience and an analytical approach. Stephenson and King, formerly colleagues in Glasgow for many years, are well suited to this difficult task, and in the main have succeeded admirably.

The book is in two parts, the first, on Investigations, contains 12 chapters, and the second, on Disorders or Diseases, 14. An appendix gives the predictive value of investigation results, some normal values and diagnoses of the 'illustrative' cases. The application, value and shortcomings of the various types of tests are discussed in Part I. The approach is necessarily selective and the philosophy of tests receives much attention. The limitations imposed by the patient and those of the test itself are stressed repeatedly. We are reminded that the neonate is fragile, so that the selection of tests must be careful and conservative, even more than in the case of the older child. In the first sentence of the first chapter we are told that EEG, the most commonly requested neurological test, should never be 'routinely' ordered, without having some sort of question in mind, and a question which the type of EEG ordered may be able to answer. Such a reminder should not be necessary, but unfortunately it *is*.

The wide clinical experience which imbues the text allows many lessons to be taught, particularly in the case illustrations. One often learns most from mistakes, which should preferably be those of others, and this principle is prominent in these brief clinical vignettes, well chosen as examples of the misreading of clinical situations and of over-investigation or misinterpretation of the result of tests. The reader will recognize familiar errors and note others as new. Some cases illustrate the importance of the 'extended family history' in which the diagnosis of a patient based on faulty data is not uncritically accepted, but family members are fully examined and a diagnosis of a serious dominant disorder is replaced by a more benign one in child and parent. The corollary, by which the diagnosis of a neurological disorder in the affected parent is made by the investigation of the index case in the child, is also illustrated.

Helpful tables list the application of various tests, for example the abnormalities of nerve stimulation and electromyography found in various conditions, and the clinical settings for those abnormalities subdivided with anatomical levels.

The chapters on disorders or diseases are firmly clinically based. In discussing the EEG in the newborn the authors stress the distinction, well described but still insufficiently recognized, between the discontinuous EEG of the normal premature baby in quiet sleep (trace alternans) and pathological burst-suppression of serious import. Many readers will be glad to pick up items of clinical information of which they were unaware or needed reminding; the occurrence of something resembling a hiccup occurring with each high-voltage burst in a burst-suppression EEG pattern in nonketotic hyperglycinaemia, the extreme nuchal hypotonia with large metopic suture in neonates with certain peroxisomal disorders, and the value of an elevated right diaphragm in the newborn with myotonic dystrophy are examples. Rare disorders deserving and receiving mention include congenital hypomyelinating neuropathy, biotinidase deficiency, hyperekplexia, the Aicardi-Goutières syndrome and a 'new' purine disorder, adenylosuccinase deficiency. References at the end of each chapter and McKusick numbers in the index direct the reader to the relevant publications.

The illustrations are well produced with their abnormal features clearly shown. CT pictures appropriately outnumber MRI, but the advantages of the latter for showing pontine and some spinal cord lesions are well demonstrated. The value of brainstem auditory evoked potentials in the diagnosis of brainstem glioma is well illustrated. Sensible comments on the value and limitations of antiepileptic drug level monitoring include the need for the laboratory, at times, to perform frequent analyses, provide answers within hours rather than days, and accept saliva when appropriate. For some readers, sadly, these desiderata will seem counsels of perfection, as will the recommending of investigations not yet available to them. Yet the authors are right to advise the ideal management, and the reader who learns from this book when *not* to request inappropriate tests, as well as when to insist upon certain investigations, will enhance the management of his patients and be in a stronger position to campaign for better facilities.

All paediatricians will benefit from reading this book, and child neurologists will gain valuable insights and perspectives from it. Not all readers will agree with everything in it, for example, with the view that ataxia with Rombergism and areflexia is a common presentation of hereditary motor and sensory neuropathy type I, but few will fail to gain from it.

I hope this book will be widely read. On the ward and in the clinic it will offer experienced guidance in the management of day to day problems, but it also deserves to be read through in its entirety to yield maximum benefit. Paediatric departments, individuals and even libraries should be able to find the cost.

E. M. BRETT

Heart and Brain, Brain and Heart. Edited by Helge Refsum, Ilmar A. Sulg and Knut Rasmussen. 1989. Pp. 467. Berlin: Springer. Price DM 198.00.

When neurologists and cardiologists sit down together they are apt, particularly if the wine is good and the cigars fragrant, to regard all that is worthwhile in medicine as their domain. This is the strength, and at times the weakness, of this edited collection of the proceedings of a symposium held in Tromsø in June 1987. There are 37 chapters divided into 8 sections, on physiology and pharmacology; the autonomic nervous system and arrhythmias; syncope and sudden death; thromboembolism and ischaemia; sleep and sleep apnoea; disease in the cardiovascular and nervous system; hypo and hyperbaric environment; and cerebral function and cardiac surgery. 'Heart' and 'brain' are interpreted broadly—vascular and neural would sometimes be more accurate, and the link between them is sometimes association, for example both have blood vessels and both are affected by changes in atmospheric pressure, rather than interaction. The canvas is so broad there is something for everyone, but inevitably this means that hardly anyone will find everything equally stimulating and worthwhile. I found the 'basic science' contributions more exciting than the clinically oriented ones, but that may simply mean I am more clinician than scientist. Conference proceedings differ from peer-reviewed articles, or even journal reviews, in that they are to a large extent freed from the constaints of available evidence and the need to present a balanced view, and often give the first glimpses of what the investigator is actually thinking. There are some fascinating ideas here, and it will be interesting to see which of their offspring will be the first to appear in the journals.

This is not a book the practising clinical neurologist or cardiologist will need to buy, and sadly it may be more than their academic counterparts can afford! It would be nice to have in the library, but it is better suited to reading than reference. Perhaps we should resurrect the old-fashioned Victorian book club—at £5 shared between 20 or so members it would be well worthwhile.

DAVID DE BONO

A History of Stroke: Its Recognition and Treatment. By William S. Fields and Noreen A. Lemak. 1989. Pp. 211. Oxford University Press. Price £30.00.

For those interested in stroke this book has many attractions. As Professor Fields and his long-term associate, Dr Lemak, have been involved in the emergence of stroke from its Cinderella role in medical research and endeavour, the book is for the authors a labour of love. Although they start with ancient history we are up to the 1960s before page 40 and the majority of the text concerns the explosion of interest in the last 30–50 years, much of which is illuminated by the authors own perspective. The impact of angiography and new imaging modalities and the impetus to research of attempted surgical remedies emerges strongly, but the central role of clinicopathological observations such as those of C. Miller Fisher is also given the weight it deserves.

The book ends with clinical anecdotes in the account of the neurological illness of famous men and women of history concentrating on Lenin, Stalin, and a series of American presidents, who seem to be stroke prone.

I think most people busy in the stroke field will enjoy this detailed history of their subject. It is salutary to realise how much of what we do was prophesied if not done before.

M. J. G. Harrison

Developmental Neuropathology. Edited by Phillipe Evrard and Alexandre Minkowsky. Nestlé Nutrition Workshop Series, Volume 12. 1989. Pp. 315. New York: Raven Press. Price $65.00.

This volume is a record of an interesting gathering of paediatricians, neuropathologists and biochemists and experimentalists held under the auspices of Nestlé. The considerable delay prior to publication is quietly alluded to, but not explained, and is clearly evident in many of the bibliographies. Nevertheless, this is a useful volume, with a surprisingly wide range, and a generous source of literature for both the novice and the nonspecialist.

The book covers a number of topics. In the first section the Massachusetts-Brussels school gives a brief but comprehensive guide to normal and abnormal brain development. There is a lot of information here, neatly packaged with good tables and clear diagrams. Literature citation is in places a little partisan, and personal theories are used somewhat dogmatically, but this is after all a meeting report, as evidenced by the discussion interludes dotted throughout the proceedings.

Other sections deal with a diverse array of topics: neurotropic factors, peroxisomes in clinical and experimental situations, gene mapping techniques, development of olivocerebellar pathways in the rat, trophic influence of serotonin, and myelinogenesis. There is also a most detailed and fascinating discussion of the role of nutrition in the synthesis of myelin lipids. This has clearly been rewritten especially for the book; its length and references would have required most of one day if delivered verbatim.

The final one-third of the book is devoted to more clinically orientated papers. Lilly Dubovitz explores visual function in neonates with evoked potentials, Hans Lou considers cerebral autoregulation, while Joseph Volpe reviews his experience with positron emission tomography (PET) in the perinatal period. Of premature infants with periventricular-intraventricular haemorrhage, those with haemorrhagic intracerebral involvement exhibit the worst prognosis. With PET scanning Volpe has been able to show that intracerebral haemorrhage is a component of a larger primary ischaemic lesion, thus confirming what pathologists have long suspected. The concluding papers are concerned with the controversial area of malnutrition and its effects on brain development.

There is plenty of nourishment in this volume, and though occasionally rendered slightly indigestible by the sheer richness of its ingredients, it overall leaves a clean taste in the mouth, a tribute to the editorial skills behind the scenes. It will be a useful sourcebook and should find its way onto many research library shelves.

Brian Harding

Advances in Growth Hormone and Growth Factor Research. Edited by E. E. Müller, D. Cocchi and V. Locatelli. 1989. Pp. 211. Heidelberg: Springer. Price DM 148.00.

There is an enormous interest in growth hormone and growth factor regulation in many fields of the biological sciences at the moment. The importance of these factors to cell growth and differentiation focuses the attention of cell biologists and oncologists, whilst their relevance to the growth and development of the whole organism makes them of fundamental interest to endocrinologists, and their role in intermediary metabolism makes them a concern of those interested in metabolic physiology and medicine.

This book, published in 1989, is devoted to the proceedings of a meeting held in Milan in 1987. It is always very disappointing when it takes so long to produce a book of this nature, especially when, as in this case, the contents are of such a high standard.

The numerous international contributors cover an enormous field of scientific endeavour, from the structure of epidermal growth factor and its receptor, to the clinical uses of growth hormone and somatostatin analogues. Herein lies one of the great strengths of this book, the demonstrated link between basic science and clinical application. This is at its most obvious when comparing the contribution of Bennett and colleagues on the characterization of natural sequence recombinant growth hormone with that of Takano and colleagues on growth hormone therapy in children with growth hormone deficiency.

All the authors can be congratulated on their clear and uncluttered presentation and on the high quality of their graphs and illustrations, taking as an example the contribution by Frohman and colleagues on the role of growth hormone-releasing hormone and somatostatin in the physiology and pathophysiology of growth hormone secretion.

The greatest limitation on this book is the time it has taken to come to publication. This is exemplified in the chapter on growth hormone-binding proteins. In this, the author presents the evidence for the identity of the main growth hormone-binding protein and the growth hormone receptor, and on balance comes down in favour of them not being identical. However, a note added in proof (!) at the end of the chapter states that structural and immunochemical evidence, published in 1988, suggests that the binding protein corresponds to the extracellular portion of the growth hormone receptor.

Despite some reservations about the usefulness of this book for researchers currently at the cutting edge of growth hormone research, it is undoubtedly extremely useful for anyone else with even a peripheral interest in growth hormone and growth factors (which surely must include almost everyone).

STAFFORD LIGHTMAN

Neuropeptide Y. Edited by Viktor Mutt, Kjell Fuxe, Thomas Hökfelt and Jan M. Lundberg. 1989. Pp. 353. New York: Raven Press. Price $119.00.

In the summer of 1988, a Nobel Conference was dedicated to the peptide, neuropeptide Y. This book, which is edited by four leaders in the field of peptide research, comprises contributions from the participants of this conference. There are 31 chapters which accurately reflect the presentations of the contributors to the Nobel Conference. The chapters are all in the 'camera-ready' format and hence the book displays a variety of type faces. The quality of reproduction of the figures is, however, excellent which is important for a subject with an anatomical basis. The camera-ready format was presumably employed to avoid a considerable lag between the timing of the conference and the appearance of the book. This is crucial for this conference which, by necessity, was attended only by invited participants and where the subject matter is progressing so rapidly. It does seem a pity that despite the camera-ready format, the book has only recently been released, more than 1 year after the conference, as I know the records of the meeting have been keenly anticipated.

The book covers the rapid growth in the knowledge concerning neuropeptide Y since the report of its discovery in 1982. The first 2 chapters, quite correctly, are written by the 2 chemists responsible for its discovery. Viktor Mutt elegantly sets the background in the context of the isolation of neuropeptide Y amongst the knowledge of other peptides and Kazukiko Tatemoto expands on the details of neuropeptide Y. Apart from these 2 chapters, the sequence of chapters in the book does not retain any historical significance but the sections are organized into the logical sequence of presentations structured by the programme of the meeting. Thus the theme of the isolation and primary structure determination is expanded in the following chapters by descriptions of the genomic structure, regulation of neuropeptide Y gene expression and the predicted tertiary structure of the peptide. The anatomical localization of neuropeptide Y within the central and peripheral autonomic nervous system is then discussed along with its colocalization with other transmitters. This is followed by a number of chapters, detailing the receptors for neuropeptide Y (their subtypes and distribution) and the pharmacological effects of the peptide both at the peripheral sympathetic neuroeffector junction and within the central nervous system. The book ends with a discussion of some of the clinical observations of disturbances in the neuropeptide Y systems.

The Nobel Conference organized by the editors of this book provided a very timely examination of the state-of-the-art of research on neuropeptide Y. The proceedings of this conference are particularly valuable, as the conference was restricted to the invited participants. The proceedings are an accurate reflection of the meeting and as such, they organize the evolution of research over the last 6 years. Research into a previously unknown substance is haphazard, and this publication allows the opportunity to pull together the various discoveries that have evolved over the last 6 years and provide some overall organization. These proceedings will be invaluable to both established neuropeptide Y research workers, and to the ever increasing number of scientists entering this area of research. It will be a valuable reference. My principal concern is that at a price of $119.00 it may well be beyond the reach of most budgets.

JANET M. ALLEN

Topographic Brain Mapping of EEG and Evoked Potentials. Edited by K. Maurer. 1989. Pp. 576. Berlin: Springer. Price DM 198.00.

This book is based on papers presented at a symposium held in Würzburg and contains 59 chapters written by a total of 141 authors from Europe, Japan and the United States. The book comprises an introductory section on the 'state of the art', followed by several papers concentrating on methodology. There is extensive coverage of clinical aspects, sections on psychophysiological aspects and evoked potential mapping, as well as a special section devoted to psychiatry. The volume finishes with two contributions on magnetoencephalography.

The brief paper 'Establishment of guidelines for the use of topographic mapping in clinical neurophysiology: a philosophical approach' written by F. H. Duffy and K. Maurer, forms a very worthy summary and introduction to the field which should not only be read but also marked and inwardly digested by anyone, neurologist, psychiatrist or clinical neurophysiologist, using or intending to use brain mapping equipment. Some of the major points are worthy of emphasis even in a brief review. For example: (1) personnel must receive additional specialized training; (2) standard EEGs should be performed and interpreted concurrently; (3) a minimum of 19 scalp electrodes should be used; (4) all systems should facilitate the detection and elimination of artefacts; (5) every system must provide means for complete calibration.

I remember Grey Walter saying in the 1960s, speaking of the Walter EEG analyser, that about 400 of these machines had been sold to EEG departments of which perhaps 4 were being used properly! Considerably more brain mapping machines have been sold but I suspect that an even smaller proportion are being properly used.

Brain mapping is based essentially on the display, as a two-dimensional diagram or 'map', of the electrical potential generated on the scalp (in the case of the EEG, or the magnetic field around the cranium in the case of the MEG). This contrasts with the conventional EEG in which the voltage at a given electrode position, or between a given pair of electrodes, is plotted with respect to time and a number of these graphs are displayed concurrently to give an idea of the behaviour of the field in different regions.

The difficulty with the two-dimensional view is to present information about the behaviour of the field with time. A great deal of empirical, clinical and diagnostic information has been gathered over the years related to the temporal behaviour of EEG potentials. Perhaps the most important is the spike, a rapid fluctuation of potential which is a clinical sign of epilepsy. The 'conventional' brain mapping technique largely ignores such inconvenient transients and concentrates on long-term averages obtained by Fourier transformation of the signals to give estimates of the amount of activity at different frequencies or in different frequency bands.

For the last decade Duffy has concentrated on techniques for comparing the unknown data with control or reference data. This volume contains a fairly extensive review (34 pages) of his work by the author. He makes the point that BEAM studies are not 'diagnostic', and that mapping will not replace the classic EEG.

E. R. John *et al.* in a later paper are less modest, claiming that '. . . multivariate statistical analyses of neurometric EEG data [can] be used for quite accurate classification of patients suffering from different psychiatric disorders'.

A less empirical stance is outlined by Freeman and Maurer under the heading of 'Advances in brain theory . . .'. This is based on Freeman's work on the olfactory bulb in animals. The paper describes a single subject cognitive experiment. What is interesting, however, is the underlying view of how brain potentials are generated: 'When a large connection of semi-autonomous elements, such as cortical neurones, is allowed or encouraged to interact extensively, each with very many others in its surround, then a cooperative entity emerges that exists as a macroscopic or large scale system having much larger spatial and temporal scales than its components.' Readers may remember the 'Ant fugue . . .' in D. Hofstadter's 'Gödel, Escher, Bach; An Eternal Golden Braid'.

D. Lehmann also bases his studies on a holistic approach but considers the EEG to consist of a sequence of brief states, each reflecting '. . . different steps or modes of information processing, which by the same token implies constraints of the reactivity of the system to subsequently arriving information'.

These latter attitudes must surely indicate the future for electrophysiological studies of the brain. All these authors emphasize the short time scales of the phenomena being considered. As Freeman and Maurer point out, '. . . only the EEG and MEG have the spatial and temporal resolution that are essential to deriving estimates of these patterns, none of the other techniques [CAT, NMR, PET, etc.] can now or foreseeably be expected to serve this purpose, because they are much too slow and coarse'.

Some method of data reduction is urgently required. Your reviewer knows only too well from personal experience that watching maps of potential distribution as they evolve is an immensely time-consuming exercise from which it is very difficult to extract the relevant features. Nevertheless I think that Duffy's view, viz. '[using a reference data base] . . . obviates the need to maintain an image of normality in one's mind', is unnecessarily defeatist.

The clinical papers in this volume vary from 'A battery approach . . .' and collections of normative data, to single case studies and reports of the follow-up of small groups. They inevitably vary in quality and will be of interest to different readers depending on their different interests.

The final papers on the MEG reflect the fact that this is a very new technique which is only just emerging from the laboratory into the clinic. I find it encouraging that the authors of both the MEG papers are placing much less emphasis on the 'dipole generator' model and are beginning to look at the patterns of magnetic activity in their own right.

This book is well produced and contains a wealth of interesting information on a very new field. It will be an essential reference work for departments of clinical neurophysiology and others who wish to make use of EEG brain mapping to further their own studies.

H. R. TOWNSEND

Clinical Electroencephalography and Topographic Brain Mapping—Technology and Practice. Edited by F. H. Duffy, V. G. Iyer and W. W. Surwillo. 1989. Pp. 304. Heidelberg: Springer. Price DM 180.00.

The authors have directed this book to physicians specializing in clinical neurophysiology, EEG technologists, and researchers in clinical neurophysiology. In that the balance of the book is towards the technological aspects of EEG recording, it is likely to appeal more to clinical neurophysiologists, for whom it will serve as an introductory text, and to EEG technicians. In my opinion, it complements rather than replaces existing textbooks on the market.

I found the overall style and approach refreshingly readable, if a little pedantic at times. Despite the title, the procedure of brain electrical activity mapping (BEAM) is covered in only 2 brief chapters, comprising 20 pages, of which 6 are coloured map illustrations. Even so, these chapters are a clear introduction to the technique and the authors include one of the foremost authorities in the field. The overall tenet seems to be that the technique, if used appropriately and cautiously, is more sensitive and objective than traditional EEG. Of the 3 case studies used to illustrate this, I was convinced in only 1 that the BEAM findings altered the management of the patient.

A major aim of the authors was to show how to obtain high quality EEGs and consequently nearly half the book is dedicated to technological aspects. Chapters 1–9 deal with basic electrical concepts, recording techniques and trouble shooting methods, with 2 further chapters (11 and 12) on electrodes and methods of localization. Difficult concepts are dealt with clearly, although there is often rapid progression from the very basic to the highly complex in the space of a few lines. Neurophysiology is covered in Chapter 10. The chapters on normal and abnormal EEGs and seizure monitoring are an overview, and the reader is referred to more specialized texts or landmark references where appropriate. The quality of the EEG illustrations is uniformly excellent and abnormalities are clearly labelled. I was surprised to find activation procedures after rather than between the chapters on normal and abnormal EEGs. A short chapter on evoked potentials follows, which serves largely as an aid to understanding the techniques underlying brain mapping.

Much of what appears in the 7 appendices could probably have been incorporated in the text; the glossary of major terms used in the text will be particularly appreciated by those new to the field.

This well produced book is competitively priced and can be recommended as an addition to the bookshelves of EEG departments and clinical neurophysiologists and EEG technicians in training.

SHELAGH SMITH

ANNOUNCEMENTS

European Neurological Society

The second meeting of the European Neurological Society will be held at the Metropole Hotel, Brighton, UK, between June 30 and July 4, 1990. On June 30 and July 1 there will be six teaching courses on: Management Problems in Neurology I and II; Movement Disorders; What you need to know about new techniques; Neuro-ophthalmology; and Neurorehabilitation. The scientific programme (July 2–4) includes five symposia (on Retroviruses and the Nervous System; Epilepsy; Basis for Recovery in Neurology; Behavioural Neurology; and Molecular Basis of Neuromuscular Disease), platform and poster sessions. Final submission data for abstracts: January 15, 1990. Further information from Concorde Services Ltd, 10 Wendell Rd, London W12 9RT, UK, tel 01 743 3106, FAX 01 743 1010.

American Association of Electrodiagnostic Medicine

The 37th Annual Scientific Meeting will be held in Chicago on September 7–8, 1990, preceded by the 13th Annual Continuing Education Course (September 6) and the AAEM Workshops (September 5). Further information may be obtained from Ella M. VanLaningham, AAEM Executive Director, 21 Second Street, SW, Suite 306, Rochester, MN 55902, USA.

Society for Research into Hydrocephalus and Spina Bifida

The 34th Annual Scientific Meeting of this Society will be held in Oviedo, Spain, on July 11–14, 1990. Further information may be obtained from Dr R. Bayston, Institute of Child Health, 30 Guildford Street, London WC1N 1EH, UK.

Third International Epileptological Symposium

A symposium on Benign Localized and Generalized Epilepsies in Early Childhood will be held in the Steigenberger Hotel, Bad Kreuznach, near Frankfurt-am-Main, FRG, on September 20–22, 1990. For further information, contact Professor R. Degen, Epilepsy Center Bethel, 4800 Bielefeld 13, FRG, or Professor F. Dreifuss, School of Medicine, Department of Neurology, Charlottesville, VA 22908, USA.

Institute of Psychiatry, University of London

A 3 day course on Advances in Affective Disorders in Old Age will be held at the Institute of Psychiatry on July 23–25, 1990, and a 2 day course on Eating Disorders on September 27–28, 1990. For further information about both courses, contact Conference Organizer, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK. Telephone 01 703 5411, extension 3170.

Fifteenth Salzburg Conference on Cerebrovascular Disease

The next meeting of the Research Group on Cerebrovascular Diseases of the World Federation of Neurology will be held in S. Margerita, Genova, Italy, on September 27–29, 1990. Further information may be obtained from Carlo Loeb, Clinica Neurologica Universita' di Genova, via De Toni 5, Genova, Italy. Telefax 0039-10-354180.

Fyssen Foundation 1990 International Prize

The general aim is 'to encourage all forms of scientific enquiry into cognitive mechanisms, including thought and reasoning underlying animal and human behaviour, into their biological and cultural bases, and into their phylogenetic and ontogenetic development'. For this purpose a substantial *International Scientific Prize* will be awarded for a major contribution to the progress of knowledge in the fields of research supported by the Foundation such as ethology, palaentology, archaeology, anthropology, psychology, epistemology, logic and the neurosciences. The discipline for the 1990 Prize is Anthropology and Cognition.

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Riyadh Armed Forces Hospital, Saudi Arabia

The Third Annual International Course on Magnetic Resonance Imaging will be held in Riyadh, Saudi Arabia, on October 14–17, 1990. For further information, contact Dr H. S. Sharif, Department of Medical Studies, Armed Forces Hospital, PO Box 7897, Riyadh 11159, Saudi Arabia.

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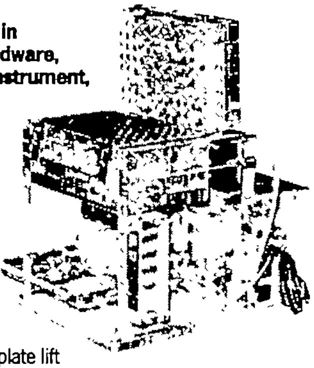

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Brain

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VOLUME 113 · PART IV · AUGUST 1990

Benign hereditary cerebellar ataxia with extensive thermoanalgesia. M. Pollock and B. Kies 857

End-plates, transmission and contractile characteristics of muscles without spindles in the hereditary sensory neuropathy of the *Sprawling* mouse. G. A. Brook and L. W. Duchen 867

Release of cold-induced burning pain by block of cold-specific afferent input. D. Yarnitsky and J. L. Ochoa 893

Type I familial amyloid polyneuropathy. A pathological study of the peripheral nervous system. G. Sobue, N. Nakao, K. Murakami, T. Yasuda, K. Sahashi, T. Mitsuma, H. Sasaki, Y. Sakaki and A. Takahashi 903

Mapping of brainstem lesions by the combined use of tests of visually-induced eye movements. I. Kato, J. Watanabe, T. Nakamura, K. Harada, T. Hasegawa and R. Kanayama 921

Effects of anterior corpus callosum section on cortical glucose utilization in baboons. A sequential positron emission tomography study. T. Yamaguchi, M. Kunimoto, S. Pappata, C. Chavoix, D. Riche, L. Chevalier, B. Mazoyer, M. Mazière, R. Naquet and J.-C. Baron 937

The origin of remyelinating oligodendrocytes in antiserum-mediated demyelinative optic neuropathy. W. M. Carroll, A. R. Jennings and F. L. Mastaglia 953

Visual loss in multiple sclerosis and its relation to previous optic neuritis, disease duration and clinical classification. W. P. Honan, J. R. Heron, D. H. Foster, G. K. Edgar, M. O. Scase and M. F. Collins 975

From covert to overt recognition of faces in a prosopagnosic patient. J. Sergent and M. Poncet 989

Hemispatial neglect in a patient with callosal infarction. A. Kashiwagi, T. Kashiwagi, T. Nishikawa, H. Tanabe and J.-I. Okuda 1005

Peripheral neuropathy in xeroderma pigmentosum. T. Kanda, M. Oda, M. Yonezawa, K. Tamagawa, F. Isa, R. Hanakago and H. Tsukagoshi 1025

Preserved recall versus impaired recognition. A case study. J. Delbecq-Derouesné, M. F. Beauvois and T. Shallice 1045

Evidence that the long-latency stretch responses of the human wrist extensor muscle involve a transcerebral pathway. D. S. Goodin, M. J. Aminoff and P.-Y. Shih 1075

Neuronal activity in the human medial temporal lobe during recognition memory. G. Heit, M. E. Smith and E. Halgren 1093

Contents continued on back cover.

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Continued on inside back cover

Brain

A JOURNAL OF NEUROLOGY

VOLUME 113 · PART IV · AUGUST 1990

Benign hereditary cerebellar ataxia with extensive thermoanalgesia. M. Pollock and B. Kies 857

End-plates, transmission and contractile characteristics of muscles without spindles in the hereditary sensory neuropathy of the *Sprawling* mouse. G. A. Brook and L. W. Duchen 867

Release of cold-induced burning pain by block of cold-specific afferent input. D. Yarnitsky and J. L. Ochoa 893

Type I familial amyloid polyneuropathy. A pathological study of the peripheral nervous system. G. Sobue, N. Nakao, K. Murakami, T. Yasuda, K. Sahashi, T. Mitsuma, H. Sasaki, Y. Sakaki and A. Takahashi 903

Mapping of brainstem lesions by the combined use of tests of visually-induced eye movements. I. Kato, J. Watanabe, T. Nakamura, K. Harada, T. Hasegawa and R. Kanayama 921

Effects of anterior corpus callosum section on cortical glucose utilization in baboons. A sequential positron emission tomography study. T. Yamaguchi, M. Kunimoto, S. Pappata, C. Chavoix, D. Riche, L. Chevalier, B. Mazoyer, M. Mazière, R. Naquet and J.-C. Baron 937

The origin of remyelinating oligodendrocytes in antiserum-mediated demyelinative optic neuropathy. W. M. Carroll, A. R. Jennings and F. L. Mastaglia 953

Visual loss in multiple sclerosis and its relation to previous optic neuritis, disease duration and clinical classification. W. P. Honan, J. R. Heron, D. H. Foster, G. K. Edgar, M. O. Scase and M. F. Collins 975

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Neuronal activity in the human medial temporal lobe during recognition memory. G. Heit, M. E. Smith and E. Halgren 1093

Contents continued overleaf

Mood disorders after stroke and their relation to lesion location. A CT scan study. A. House, M. Dennis, C. Warlow, K. Hawton and A. Molyneux 1113

Impaired memory for new visual forms. J. R. Hanley, N. A. Pearson and A. W. Young 1131

Movement variability and bradykinesia in Parkinson's disease. M. R. Sheridan and K. A. Flowers 1149

Perceptual and conceptual mechanisms in neglect dyslexia. Two contrasting case studies. M. Behrmann, M. Moscovitch, S. E. Black and M. Mozer 1163

Processing of local and global musical information by unilateral brain-damaged patients. I. Peretz 1185

Lyme neuroborreliosis. Peripheral nervous system manifestations. J. Halperin, B. J. Luft, D. J. Volkman and R. J. Dattwyler 1207

Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. Th. De Broucker, P. Cesaro, J. C. Willer and D. Le Bars 1223

Book reviews 1235

Announcements 1249

Brain (1990), 113, 857–865

BENIGN HEREDITARY CEREBELLAR ATAXIA WITH EXTENSIVE THERMOANALGESIA

by M. POLLOCK *and* B. KIES

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SUMMARY

A New Zealand family with 3 members affected by late onset hereditary cerebellar ataxia is reported, distinguished by the development of near global thermoanalgesia. Because proprioception and autonomic function were preserved, and ataxia only slowly worsened, this proved to be a benign syndrome. The pattern of sensory loss indicated a 'length-dependent' neuropathy. Evaluation of sural nerve biopsy revealed a marked loss of axons, especially of those with diameters 1–7 μm and 0.2–1.5 μm. It therefore seemed likely that impairment of pain and temperature in the syndrome resulted from a loss of primary sensory afferents. It is concluded that this family represents a previously unrecognized variant and that the spectrum of hereditary ataxias needs to be widened to include an associated severe but selective loss of pain and temperature sensation.

INTRODUCTION

The majority of patients with late onset hereditary cerebellar ataxia have no sensory complaints. When sensory symptoms occur, they are of minor degree with sensory signs typically restricted to abnormalities of vibration and joint position sense (Harding, 1984). This report describes a variant of late onset ataxia with a near global loss of pain and temperature.

CASE REPORTS

Case 1

J.M., the proposita, a 71-yr-old widow (fig. 1), presented with a 6 yr history of staggering gait. This had been only slowly progressive and she was still able to live independently and drive a manual car. She had also noted widespread burning sensations, in the legs for 6 yrs, in the fingers for 3 yrs and over the vertex of the scalp for 2 yrs. Occasionally she had been surprised to find blood in her slippers as a result of unrecognized injuries. She had had no exposure to toxins and had never taken alcohol in excess. Her mother, who died at the age of 59 yrs, had complained of numb fingers, but had had no obvious ataxia.

On neurological examination, her higher functions were normal. Using a stick, she walked on a broad base with titubation of the trunk and head. Her speech was mildly dysarthric. Fundoscopy was normal but a fine jerk nystagmus was present on horizontal gaze to either side. There was no loss of ocular saccades, although smooth pursuit movements were impaired. Mild wasting and weakness were present in the small muscles of the hands and feet and in the hip flexors, with normal limb tone. Tendon reflexes were normal

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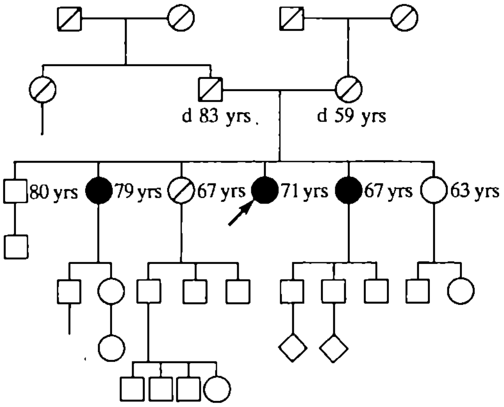

FIG. 1. Pedigree of family.

in the arms but increased without clonus at the knees. The right ankle jerk was barely elicitable, and the left ankle jerk absent. Both plantar reflexes were unresponsive. There was moderate ataxia in all limbs with proximal intention tremor.

The most striking findings were on sensory examination. The only parts of the body where pin prick was appreciated normally were the lateral face, neck and paraspinal area (fig. 2). Pin prick and temperature sensation were lost over the central scalp and face, and in the limbs below the elbows and groin. These modalities were impaired to a lesser degree above the elbows and over the lateral trunk to the level of the clavicles. Touch sensation was globally impaired in the same pattern but not lost. Vibration sense was impaired below the wrists and knees, but position sense was preserved to the finest movements of toes and fingers. Peripheral nerves were neither palpably enlarged nor tender.

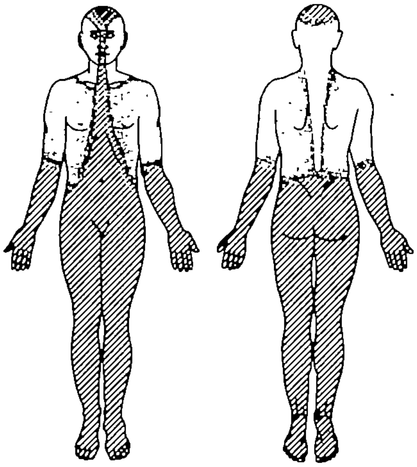

FIG. 2. Pin prick and temperature sensation in proposita. Stippling = decreased; diagonals = lost.

Laboratory investigations. The following were normal: routine haematology, plasma urea and electrolytes, thyroid function, serum immunoglobulins and protein electrophoresis, vitamin B_{12}, serum folate, fasting blood sugar, gamma glutamyl transferase, serum cholesterol, triglycerides, urinary porphyrins, blood lead, ANA tests, syphilis serology, leucocyte arylsulphatase, and hexosaminidase A and galactocerebrosidase activities.

Radiology. Computerized tomography of the head showed prominent cerebellar sulci, without pontine atrophy or hypodense lesions in white matter.

Neurophysiological investigation. Median and sural sensory action potentials (SAPs) were absent (Table 1). The superficial radial SAP had a low amplitude and mildly reduced conduction velocity, but was not dispersed. Median and common peroneal motor conduction velocities and amplitudes were normal, with no dispersion or conduction block (Table 2). There was evidence of mild chronic denervation in biceps brachii, first dorsal interosseous and tibialis anterior muscles. Brainstem auditory evoked potentials were normal.

TABLE 1. SENSORY NERVE CONDUCTION

	Median nerve		*Superficial radial nerve*		*Sural nerve*	
Case	*CV*	*Amp*	*CV*	*Amp*	*CV*	*Amp*
1	Absent		54	2	Absent	
2	Absent		Absent		ND	
3	48	1	50	1	38	1
Normal >	51	10	56	10	45	4

CV = conduction velocity ($m \cdot s^{-1}$); Amp = amplitude (μV); ND = not done.

TABLE 2. MOTOR NERVE CONDUCTION

	Median nerve		*Peroneal nerve*	
Case	*DL*	*CV*	*DL*	*CV*
1	3.1	51	5.0	42
2	4.5	48	5.6	40
3	2.5	48	4.4	40
Normal	<3.7	>48	<4.5	>40

DL = distal latency (ms); CV = conduction velocity ($m \cdot s^{-1}$).

Autonomic function. Sweating, examined on the dorsal surface of the feet by the quantitative acetylcholine sweatspot test, showed a normal density of innervated sweat glands (Ryder *et al.*, 1988). The histamine flare test was normal, causing a wheal and erythema. Blood pressure, lying, was 120/82 mmHg and with 60° tilt was 115/72 mmHg. Carotid massage caused bradycardia. Sinus arrhythmia was slightly reduced at rest with an R-R interval ratio during expiration and inspiration of 1.03 (normal > 1.06; Smith, 1982).

Case 2

I.D., an abstemious 79-yr-old sister of the proposita (fig. 1), had at the age of 51 yrs first experienced incoordination of gait. This had slowly worsened and been exaggerated in the dark. She was still able to walk 200 yards each week for her groceries without a stick. In the same period she had felt a 'muzziness' in her hands which had gradually spread proximally. Later she had been intermittently surprised to find her hands bleeding from unrecognized trauma. For 2 yrs she had experienced a burning sensation below the knees and an inability to feel hot or cold in the legs.

On examination, cognitive function was preserved and the fundi were normal. There was mild slurring, but no scanning of speech. Ocular saccades were preserved, but bilateral downbeat nystagmus was present, unassociated with oscillopsia. The cranial nerves were otherwise normal. Moderate weakness, seen only in the upper limbs, was greater proximally, with mild hypotonicity and wasting. On finger-nose testing there was past-pointing with a proximal side-to-side tremor on heel-shin testing. She walked with a wide base and truncal titubation. Tendon reflexes were symmetrically present except for the ankle jerks. Both plantar responses were flexor.

Sensory examination showed a near global impairment of pain and temperature appreciation. Pain sensation was more severely affected, being lost in the limbs, trunk and in a central 'muzzle-like' distribution on the face, and impaired in the lateral face and paraspinally. Temperature sensation was lost distal to the groin, moderately impaired in the arms and trunk, and only slightly impaired in the central face and paraspinal area. Light touch was impaired only in the fingers and feet. Vibration sense was absent below the anterior superior iliac spines, but position sense was normal.

Neurophysiological investigation (Tables 1 and 2). This showed absent median, ulnar and superficial radial SAPs. Median and common peroneal motor conduction velocities were at the lower limit of normal with no dispersion or conduction block. The median distal motor latency was slightly prolonged. Marked chronic denervation was found in the first dorsal interosseous muscle with motor unit potential amplitudes increased to 8 mV. Moderate chronic denervation was found in the extensor digitorum communis muscle, but a normal electromyogram was recorded from biceps brachii.

Case 3

C.L., a 67-yr-old sister of Case 1 (fig. 1) remains ambulatory despite a 10 yr history of slowly progressive difficulties with gait. She walked without support on a broad base with marked truncal titubation. There was no dysarthria, but she had a fine horizontal jerk nystagmus on gaze to left and right. As with her affected sisters, intellect was preserved. The remainder of the cranial nerve examination, including fundoscopy, was normal. Muscle power and tone were normal and the tendon reflexes present except for the ankle jerks. The plantar reflexes were nonresponsive. There was ataxia on finger-nose and heel-shin testing, and rapid alternating movements were impaired bilaterally. Peripheral nerves were not enlarged or tender. She was normotensive without postural hypotension.

Sensory findings mirrored those seen in her affected sisters. Pin prick and temperature appreciation was lost centrally over the face, scalp and trunk, and lost in the limbs distal to the groin and elbows. Elsewhere impaired pain and temperature sensation shaded to normality in the lateral face, neck and in the paraspinal area. Vibration sense was absent in the toes and reduced at the ankles, but position sense was intact.

Neurophysiological investigation (Tables 1, 2). This showed markedly reduced SAPs in the median, superficial radial and sural nerves (1 μV). Sensory conduction velocities were slightly reduced without dispersion. Median and common peroneal motor conduction velocities and amplitudes were normal.

MORPHOLOGICAL INVESTIGATIONS

Nerve biopsy

A whole sural nerve biopsy was obtained from the proposita under local anaesthesia at the ankle level in June, 1987. Age-matched control sural nerve had been previously obtained from unpaid volunteers who had given informed consent (Declaration of Helsinki) after normal neurological evaluation and normal nerve conduction studies.

Methods. The processing of sural nerve tissue and its morphometric evaluation was carried out according to previously described methods (Pollock *et al.*, 1983*a*). In short, the specimen was fixed in 2% glutaraldehyde, washed in buffer and postfixed in 1% osmium tetroxide. After dehydration through graded concentrations of alcohol, the specimen was embedded in epoxy resin. Semithin sections (1 μm) for light microscopy were stained with 1% phenylenediamine or 1% methylene blue. Thin sections for electron microscopy (Philips 410) were stained with 12.5% methanolic uranyl acetate and lead citrate. Unmyelinated axon counts were undertaken from 4 different fascicles, from an area comprising 15% of the total fascicular area, at a magnification of ×14 000. A diameter histogram of 300 unmyelinated axons was obtained from photographic enlargements (×12 000), using a Zeiss TGZ-3 particle size analyser set on a linear scale. Diameter histograms of both myelinated nerve fibres and unmyelinated axons were compared with controls using the Kolmogorov-Smirnov test (Siegel, 1956). Single fibre preparations were obtained by teasing in glycerol and graded (Pollock and Dyck, 1976); 68 fibres were isolated. The kurtosis of the binomial distribution was used to test whether abnormal internodes were randomly dispersed amongst all nerve fibres and graded descriptively to assess for an increased frequency of adjacent abnormal internodes.

Results. Analysis of teased nerve fibres (a total of 756 internodes) revealed 59% were normal, with an absence of degenerating fibres (type E). By contrast, there was a high incidence (38%) of teased fibres exhibiting remyelinated internodes (type F) with at least a 50% reduction in myelin thickness. An analysis of the distribution of these remyelinated internodes in comparison with control values indicated a nonrandom distribution ($P < 0.001$) and an increased frequency of adjacent remyelinated internodes ($P < 0.001$). Many thinly myelinated internodes were intercalated. Demyelinated internodes were seen in only 3% of the patients' teased fibres.

Transverse sections of sural nerve showed a significant reduction in the number of small and large myelinated fibres (fig. 3), both in density (Table 3), as well as in the number per whole nerve. Many surviving myelinated fibres had inappropriately thin myelin in relation to axon diameter. Three of the 6 fascicles in the nerve contained Renaut corpuscles. There were no amyloid deposits and no inflammatory infiltrates. The myelinated fibre diameter histogram was significantly shifted to the left compared with control nerve ($P < 0.001$), due to a reduction in the large fibre peak (fig. 4).

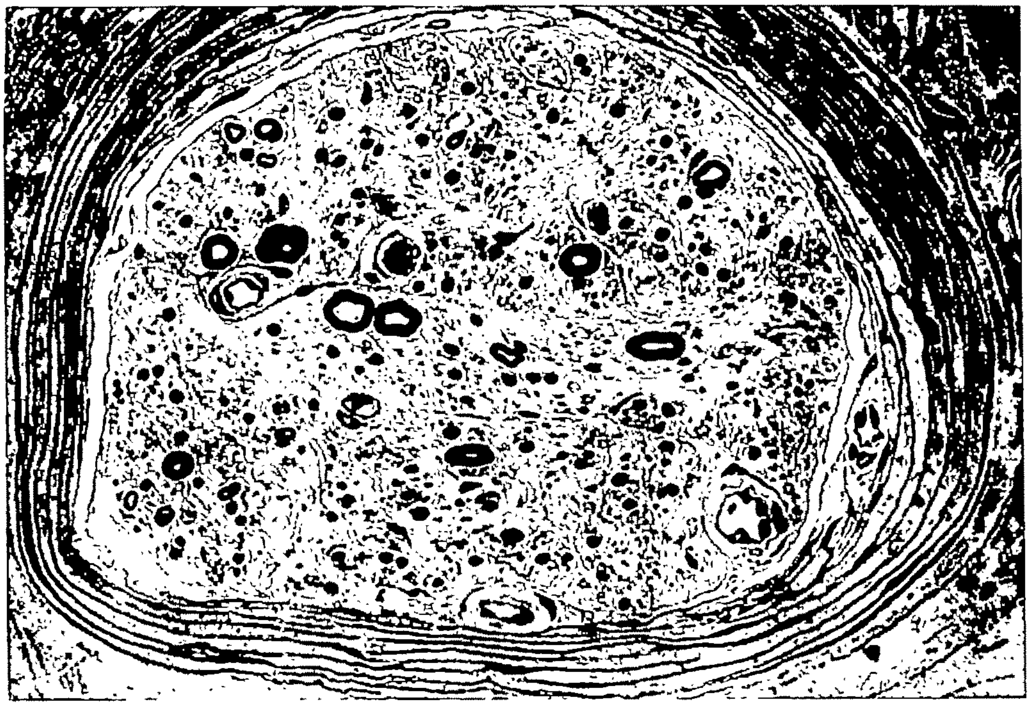

FIG. 3. Transverse section of sural nerve from *Case 1* showing marked reduction of myelinated fibres. ×500.

TABLE 3. SURAL NERVE FIBRE DENSITY (per mm^2)

	Myelinated fibres	*Unmyelinated fibres*
Case 1	568	16 549
Controls (±SD)	7340 (± 1630)	25 059 (±3729)

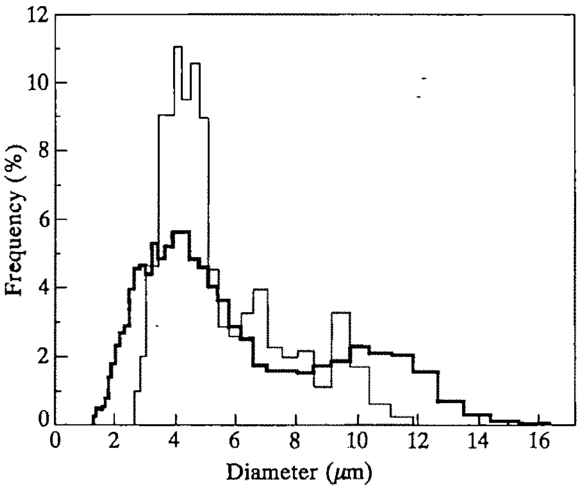

FIG. 4. Diameter histograms of myelinated sural nerve fibres from *Case 1* (hatched) and controls (nonhatched).

Quantitative electron microscopy revealed a significant but less severe reduction in the densities of unmyelinated nerve fibres (Table 3). The unmyelinated diameter histogram when compared with control nerves was significantly shifted to the right ($P < 0.001$) as a result of a predominant loss of sensory fibres in the drC category (0.2–1.5 μm). (fig. 5).

There was no excess of lipofuscin and no endoneurial cytoplasmic inclusions evident in electron microscopic examination of the sural nerve.

DISCUSSION

All 3 affected family members showed a remarkable stereotype of clinical findings heralded by a progressive ataxia beginning in the sixth or seventh decades. Sensory impairment soon began distally and gradually spread proximally to culminate in a near global loss of pain and temperature appreciation. Because ataxia progressed slowly and proprioception and autonomic function were preserved, it proved to be a benign form of hereditary ataxia. This was typified by the oldest affected sister who, despite a 28 yr history of ataxia, remains ambulent and independent. In keeping with the indolent course, nerve biopsy revealed no active myelinated fibre breakdown. This result is in agreement with electrophysiological and histological evidence of chronic axonal neuropathy in the spinocerebellar degenerations of non-Friedreich type (McLeod and Evans, 1981; Bennett *et al.*, 1984; Dyck, 1984). Chronic axonal atrophy would also account for the present finding of a high incidence of clustered remyelinated internodes

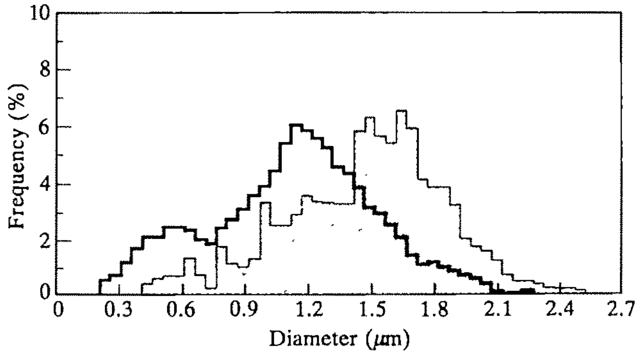

FIG. 5. Diameter histograms of unmyelinated sural nerve fibres from *Case 1* (hatched) and controls (nonhatched).

(Dyck, 1982), although this finding could equally well have resulted from juxtaposed remyelinated internodes. Both peripheral nerve degeneration and segmental demyelination have been previously described in patients with olivopontocerebellar atrophy (Carenini *et al.*, 1984).

A number of hereditary disorders, which present as spinocerebellar syndromes with neuropathy, namely Krabbe's disease (Thomas *et al.*, 1984), adrenoleukomyeloneuropathy (Marsden *et al.*, 1982), adult chronic G_{M2} gangliosidosis (Rapin *et al.*, 1976) and ceroid lipofuscinosis (Wisniewski *et al.*, 1988) were excluded.

The distribution of sensory loss supports the view of a length-dependent peripheral neuropathy in this hereditary ataxia (Sabin, 1986). In the head, maximum sensory impairment in the central face and over the vertex of the scalp suggests involvement of the terminal tributaries of the ophthalmic, maxillary and mandibular divisions of the trigeminal nerves and of the C2 roots. Similarly, the dominant sensory loss in the anteromedial abdomen, with relative or absolute sparing in the paraspinal region, is also indicative of a length-dependent neuropathy.

Traditionally, mammalian afferent sensory fibres from thermoreceptors and nociceptors have been divided into two populations based on axon diameter; myelinated fibres with diameters of 1–7 μm (type AIII) and unmyelinated axons with diameters of 0.2–1.5 μm (drC) (Berthold, 1978). Both categories of sural nerve fibres with these axonal diameters were severely depleted in this investigation. Generalizing from this pathology, it is likely that global thermoanalgesia in this syndrome results from a diffuse loss of primary sensory afferents.

Ruffini joint and pacinian endings give rise to some of the largest sensory afferents (AII) with diameters of 5–13 μm (Boyd and Davey, 1968). Studies of sural nerve before and following biopsy have established that this nerve contains proprioceptive fibres innervating the distal joint of the fifth toe (Pollock *et al.*, 1983*b*). It is therefore surprising that with so few myelinated fibres in the AII afferent category surviving, position sense was completely preserved. A possible explanation stems from the slow ingravescent course of this hereditary ataxia. This might have allowed time for collateral sprouting of large myelinated afferent fibres within the neuraxis and thereby the central amplification of proprioceptive input. A similar mechanism has been suggested to account for the presence of large evoked potentials in type II hereditary sensory neuropathy (Nukada *et al.*, 1982).

In this kinship, 3 of 6 siblings were clinically affected, with a suggestion that the mother, who died aged 59 yrs, had early clinical involvement. The likely mode of inheritance is, therefore, autosomal dominant, although the uncertainty of the maternal phenotype does mean that an autosomal recessive inheritance cannot be entirely excluded.

Semiology in this family would favour dominant pathology in dorsal root ganglia and cerebellum. Since, however, it has proved impossible to predict accurately on clinical evidence alone the extent and type of neuropathology in the hereditary ataxias, morphological categorization of this syndrome must await autopsy examination.

There is increasing evidence of peripheral nerve involvement in the system degenerations of the cerebellum (Dyck, 1984; Bennett *et al.*, 1984). Nousiainen *et al.* (1988), on the basis of an electromyographic and muscle biopsy study in late onset spinocerebellar ataxia, have concluded that there is always involvement of lower motor neurons that neither correlates with the duration nor severity of the disease. Despite the frequency of peripheral nerve lesions in late onset hereditary ataxia, paraesthesiae are infrequent and sensory abnormalities are usually restricted to impaired vibration and kinaesthetic sensation (Harding, 1982).

Widespread loss of pain and temperature sensation in this study suggests that the spectrum of sensory loss in late onset hereditary ataxia needs to be widened and that this disorder should be considered in the differential diagnosis of diffuse thermoanalgesia.

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END-PLATES, TRANSMISSION AND CONTRACTILE CHARACTERISTICS OF MUSCLES WITHOUT SPINDLES IN THE HEREDITARY SENSORY NEUROPATHY OF THE *SPRAWLING* MOUSE

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SUMMARY

In the mutant mouse *Sprawling*, a deficiency of sensory ganglion cells is associated with a failure of the development of spindles and tendon organs particularly affecting muscles of the hindleg. Electrophysiological and morphological investigations were made on nerve, muscle and the neuromuscular junction of soleus and extensor digitorum longus (EDL). It was found that the absence of sensory innervation had no effect on the development of muscle bulk, on the fibre diameters or on histochemical profiles. The elimination of polyneuronal innervation proceeded at the normal rate and was complete by 3 wks of age. The strength of contractile responses and the number of motor units were normal in both muscles. End-plate areas were measured and the size distribution found to be normal in soleus. In EDL, however, there was a preponderance of small end-plates and a relative deficiency of large ones. This was associated with an abnormally low frequency of miniature end-plate potentials and of the mean quantal content of transmission. There was also a reduction in the complexity of the postsynaptic specialization at end-plates in the EDL. Localized axonal swellings packed with neurofilaments were observed in preterminal motor nerve fibres, which suggested an abnormality of axonal transport. There was no evidence of denervation of muscle fibres. The contractile characteristics of soleus and EDL were still distinguishable as slow and fast-twitch, respectively, despite the abnormalities found, and it seems likely that impulse traffic in the lower motoneuron is only marginally affected, if at all. An abnormality of axonal transport may be responsible for the inability of motoneurons to maintain large end-plates in fast-twitch muscles.

INTRODUCTION

The neurological mutant mouse *Sprawling* (gene symbol *Swl*) has a dominantly inherited abnormality of sensory pathways. Excessive ganglion cell necrosis during fetal development causes a congenital deficiency of afferent input to the spinal cord (Duchen, 1975; Duchen and Scaravilli, 1977*a*). Sensory roots have reduced numbers of large myelinated axons and there is a generalized reduction in the number of muscle spindles, Golgi tendon organs and pacinian corpuscles. Muscles of the hindleg are totally lacking in spindles. Dorsal root ganglion cells are abnormally few in number and those which remain appear chromatolytic, without, however, any morphological evidence of axonal degeneration (Duchen and Scaravilli, 1977*b*; Scaravilli and Duchen, 1980*a*).

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Quantitative observations on *Swl* mice indicated that there is an abnormally high rate of ganglion cell death during fetal development (Scaravilli and Duchen, 1980*b*), so that by the second day after birth, motoneurons already lack a considerable proportion of their afferent influence. There have been no investigations in this mutant on the effects of the sensory deficiency on motor nerve and muscle function. It is known that the development of skeletal muscle is dependent on its innervation and that the contractile properties are largely determined by the innervating motoneurons (*see* Jolesz and Sreter, 1981). The physiological and morphological properties of adult CNS neurons including spinal motoneurons have been reported to be altered by the removal of part of their afferent input (Bernstein and Bernstein, 1973; Kjerulf *et al.*, 1973; Nelson and Mendell, 1979; Gustafsson *et al.*, 1982).

This paper describes a physiological and morphological study of the development and maintenance of neuromuscular transmission and the functional properties of fast and slow-twitch muscles in the hindleg of *Swl* mice.

MATERIAL AND METHODS

Animals

Since this is a dominantly inherited disorder, litters obtained from mating *Swl* females with normal males contained 50% affected offspring. *Swl* pups could be recognized as early as postnatal day 6 by abnormal flexion of the hindlimbs when the mouse is lifted by the tail.

Animals of either sex aged 6–400 days were studied, including 95 affected and 80 normal mice for the morphological study and 40 *Swl* and 40 normal mice in the physiological studies. In each group 20 animals were used for studying mechanical responses and 20 for electrophysiological recordings.

Physiological methods

Mice were anaesthetized with sodium pentobarbitone (60 mg/kg by intraperitoneal injection) and killed by cervical dislocation. The right hindlimb was removed and soleus and extensor digitorum longus (EDL) muscles, each with a length of its nerve, were dissected out under cooled oxygenated Ringer solution. The composition of the Ringer solution was (in mmol): NaCl, 115; KCl, 3.5; $MgSO_4$, 1.0; $NaHCO_3$, 25; $CaCl_2$, 2.0; glucose, 11.0. The solution was saturated with 95% O_2/5% CO_2 and the pH adjusted to 7.4. Muscles were then transferred to an organ bath through which there was a constant flow of Ringer solution at room temperature (20–22°C).

Mechanical responses were recorded with a Bioscience UF1 isometric tension transducer. Supramaximal direct stimulation was applied by passing square wave pulses (100 V, 0.5 ms) across the belly of the muscles with fine platinum wires. Indirect stimulation (up to 30 V, 50 μs) was applied with purpose built suction electrodes. The fatigability of muscles was measured by direct stimulation of soleus (20 Hz, 10 s) and EDL (45 Hz, 10 s) and the ratio of tension maintained at the end of stimulation to that developed at the onset of stimulation was calculated as a percentage. This is referred to as the fatigue index. All muscles were stretched to the optimal length necessary for maximum tension development.

The *number of motor units* in muscles was determined from recordings to twitch tensions, evoked by graded intensities (0–30 V) and durations (50 μs–0.5 ms) of nerve stimulation at 0.20 Hz. This process was repeated with decreasing as well as increasing intensities of stimulation until reproducible estimates of the number of units had been obtained.

Electrophysiology. Unless otherwise stated, intracellular recordings were made from approximately 30 superficial muscle fibres from each preparation using standard electrophysiological techniques (Fatt and

Katz, 1951). Glass microelectrodes (10–50 MΩ) were filled with 3M KCl and signals were amplified and displayed on Tektronix 5113 storage oscilloscopes. Recordings were made of spontaneous miniature end-plate potentials (MEPPs), and evoked end-plate potentials (EPPs) and of the resting membrane potential (RMP).

Hard copies of focal MEPPs and EPPs were made on a Gould 2200S pen recorder, were measured on a Kontron MOP-AMO3 image analyser linked to an RML 380Z computer and were corrected to a standard RMP by the method of Katz and Thesleff (1957).

The *mean quantal content* (MQC) of neuromuscular transmission was estimated by the method of variance (Boyd and Martin, 1956; Elmqvist and Quastel, 1965) from a train of 60 EPPs evoked by stimulation of the nerve at 20 Hz in preparations partially blocked by the presence of 1–2 μM d-tubocurarine. The first few EPPs, which show the normal run-down in amplitude, were discarded and the MQC calculated after the amplitude was stabilized.

The extent of *multiple innervation* of single end-plates was tested physiologically by stimulating the nerve to a curarized preparation at 1.0 Hz, varying the strength or duration of the pulse in order to recruit multiple inputs (Redfern, 1970) and noting the proportion of end-plates tested which showed evidence of polyneuronal innervation.

Morphological methods

Mice under pentobarbitone anaesthesia were perfused with fixative through the left ventricle.

Paraffin histology. The fixative used was formol-calcium (10% formalin in 1% calcium acetate) followed by FAM (formaldehyde 1 part; glacial acetic acid 1 part; methanol 8 parts). After fixation, muscle blocks were taken from fore and hindlimbs, processed and embedded in paraffin. Transverse and longitudinal sections were stained with haematoxylin-eosin, haematoxylin-van Gieson and by the silver impregnation method of Marsland *et al.* (1954) for axons.

Cholinesterase activity and axons. Mice were perfused with cold formol-calcium, after which muscle blocks containing soleus and EDL were dissected out, frozen and 20–30 μM sections cut in a cryostat. Sections were stained with bromoindoxyl acetate (BIA) for cholinesterase combined with silver impregnation for axons (Pestronk and Drachman, 1978).

Muscle fibre histochemistry. Fresh unfixed muscles were snap-frozen and transverse cryostat sections stained for myosin ATPase activity following acid (pH 4.3 and 4.6) or alkaline (pH 10.2) preincubation and for succinate dehydrogenase enzyme activity (Pearse, 1985).

Electron microscopy. Anaesthetized mice were perfused with cold (4° C) Karnovsky (1965) solution. Blocks of muscle were postfixed in 1% osmium tetroxide, dehydrated in graded ethanol and embedded in Araldite. Longitudinal 1 μm sections were stained with toluidine blue to localize the end-plate region. Ultrathin sections were stained with lead citrate and uranyl acetate and examined in a JEOL 100CX electron microscope at 80 kV.

Muscle fibres in soleus and EDL of 1–5 day-old mice were counted from electron micrographs of the midbelly region of whole muscles cut in transverse section and mounted on formvar coated single-slot grids. Muscle fibre counts from older muscles were made from haematoxylin-eosin stained transverse sections of the midbelly region of fixed, paraffin-embedded muscles.

Morphometry. Morphometric analysis of muscle fibre diameters and of motor end-plate areas was carried out using the bit-pad of a Kontron AMO3 image analyser linked to an RML 380Z computer. Muscle fibre diameters were calculated from their measured areas assuming circularity.

Analysis of a number of motor end-plate parameters (Table 5) defined by Engel and Santa (1971) and Santa and Engel (1973), was made from profiles of neuromuscular junctions. Specimen grids were adjusted to a standard height and the magnification calibrated with a grating replica. Each end-plate was photographed and prints enlarged to a final magnification of 30,000. Each profile of an axonal terminal with its related postsynaptic specialization was considered as an individual end-plate and was measured using the image analyser linked to the RML 380Z computer.

RESULTS

Clinical observations

Affected mice could be recognized as early as 6 days of age by the flexion of hindlimbs when the animal was lifted by the tail. The clinical appearance of affected adults was quite variable. At rest, severely affected mice appeared to be sitting on their haunches due to the abnormal extension of the hindlimbs pointing forward under the trunk. The ataxic gait of these animals often involved swinging the rather stiff hindlimbs in an arc and gave the impression of a wide based gait. Less severely affected mice could be identified only by the hindlimb flexion when the animal was raised by the tail, or by testing the ability of the animal to support itself on a wide-mesh wire grid. All affected mice tended to miss the wire grid with their paws and were unable to support themselves adequately. Climbing the wire bars of the cages in which the animals were housed was usually solely dependent on the use of their forelimbs while the hindlimbs dangled uselessly below the animal.

Body and muscle weight

Despite the often severe abnormality in motor control, *Swl* mice were able to feed normally and adult mice attained a normal body weight. The mean body weight of *Swl* mice aged between 56 and 380 days was 28.8 ± 5 g (n = 12) and that for age-matched normal mice was 30 ± 4 g (n = 10).

The development and maturation of the weight of *Swl* soleus and EDL muscles appeared to be unaffected. The rate at which muscle weight increased over the first 3 postnatal weeks and the muscle weights of the adults were similar to the normal (fig. 1A, B).

Time course of elimination of polyneuronal innervation

The time course of synaptic elimination in neonatal muscles was assessed by physiological and morphological methods. The intracellular recordings from the end-plate region of muscles showed that successive stimuli of increasing intensity generated incremental steps in the EPP amplitude. These incremental steps had discrete electrical thresholds. Counting the number of incremental steps in the EPP gives only an estimate of the minimum number of inputs as the contribution made by small, weak nerve terminals may be masked by the larger responses of stronger inputs. The number of inputs to each end-plate was not routinely counted. In the youngest mice studied the small size of muscle fibres made it difficult to obtain stable intracellular recordings and the calculation of the proportion of end-plates with multiple innervation was made from between 10 and 30 fibres.

The physiological data were complemented by the morphological observations made of the motor end-plates and the nerves innervating them. End-plate cholinesterase is stained pale blue by the BIA technique and the translucent nature of the stain allows the arborizations of the silver-impregnated terminals to be visualized. At least 60 end-plates in which the innervating axons could be clearly visualized were counted in

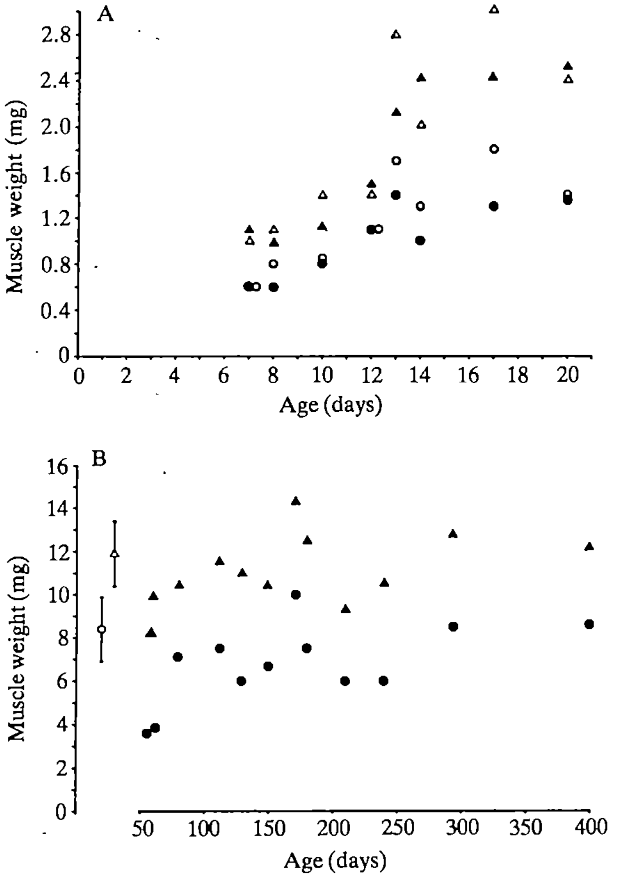

FIG. 1. Changes in muscle weight with age of normal soleus (open circles), normal EDL (open triangles), *Swl* soleus (filled circles) and *Swl* EDL (filled triangles). A, days 7–20, normal and *Swl* muscles grow at the same rate. B, days 50–400, adult *Swl* muscles attain weights similar to the normal. Mean ± SD of normal soleus (open circles) is 8.4 ± 1.4 mg (n = 10), normal EDL (open triangles) is 11.4 ± 1.5 mg (n = 10).

each muscle. At 6 and 8 days most of the end-plates were innervated by several axons and even at 14 days multiple innervation was found in 10–20% of muscle fibres (fig. 2A, B). Although physiological results indicated that most of the end-plates were innervated by single motor axons, the BIA stain showed that a small but significant proportion of end-plates was still dually innervated. The slightly higher estimate of polyneuronal innervation made from the morphological observations, compared with those obtained physiologically, may reflect the temporary presence of 'silent' motor nerve terminals at a stage just prior to retraction. Similar findings were reported by O'Brien *et al.* (1978) and Zelená *et al.* (1979) in normal rats. It was found that multiple innervation of both normal and *Swl* soleus and EDL fibres was eliminated over the first 3 wks.

Determining the number of muscle fibres in neonatal muscles required both light and electron microscopy. Muscles removed from mice aged 7 days or older were large enough and their fibres sufficiently separated from one another to allow accurate counting by light microscopy. Counting fibres in muscles removed from mice aged 5 days or younger was more difficult. In these muscles, fibres were of variable size and were often closely

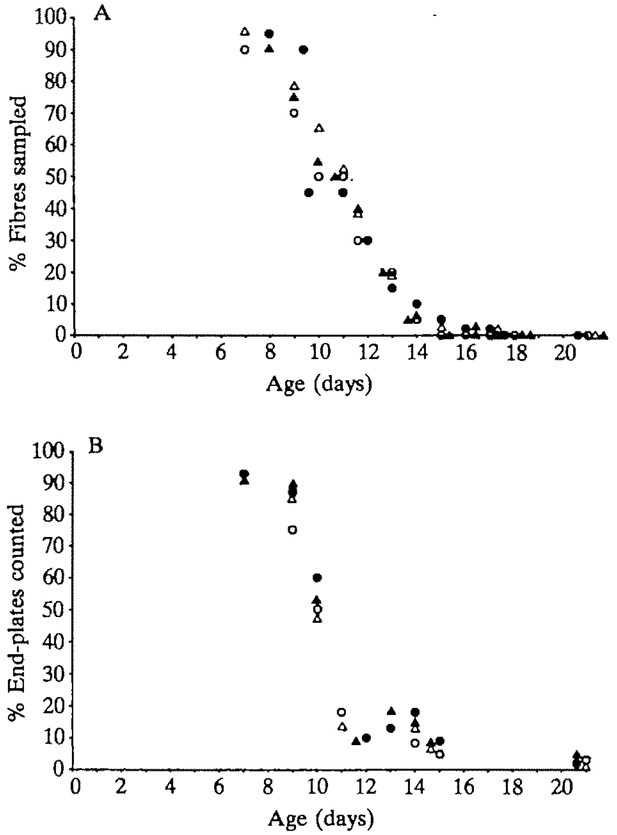

FIG. 2. Physiological (A) and morphological (B) assessment of the proportion of multiply innervated end-plates sampled in early postnatal normal soleus (open circles), normal EDL (open triangles), *Swl* soleus (filled circles) and *Swl* EDL (filled triangles) muscles. A, proportion of fibres showing complex end-plate potentials; each point represents the proportion of at least 30 fibres except those at 7 and 8 days where 10–15 fibres were sampled. B, proportion of end-plates in which multiple inputs were clearly observed. There is no obvious difference between *Swl* and normal muscles in the rate of synapse elimination.

apposed to one another; thus it was necessary to prepare a montage of low magnification electron micrographs of the cross-section of whole muscles to count the fibres. All cell profiles containing substantial amounts of myofilaments were counted. The number of fibres in normal and *Swl* soleus and EDL appeared to be remarkably constant (Table 1). The numbers of fibres counted in 1 day and 380 day normal soleus muscles were 682 and 742, respectively, and the numbers for normal EDL of the same ages were 1050 and 986, respectively, changes which cannot be regarded as significant. The development of muscle mass was clearly due to the growth of existing muscle fibres rather than the postnatal increase in the number of fibres. There was no significant difference between the number of muscle fibres of normal and *Swl* soleus or normal and *Swl* EDL ($P > 0.10$ for both comparisons; Student's t test).

Mechanical responses

It was found that the development of strength of twitch or tetanic contractions to direct stimulation was unaffected in *Swl* soleus and EDL (fig. 3A, B). The twitch (1 Hz) and tetanic (45 Hz) responses of fast-twitch EDL appear to develop at a greater rate than those of slow-twitch soleus (1 Hz and 20 Hz) during the first 3 wks. Comparison of

TABLE 1. NUMBER OF MUSCLE FIBRES IN SOLEUS AND EXTENSOR DIGITORUM LONGUS OF NORMAL AND *Swl* MICE

	Normal		*Swl*	
Age (days)	*Soleus*	*EDL*	*Soleus*	*EDL*
1	682	1050	781	957
5	756	892	729	1050
7	704	1150	732	1085
8	767	1037	795	972
14	795	983	619	1159
17	650	1028	632	880
30	633	982	639	1080
40	659	1198	596	958
60	687	1034	684	1203
84	659	953	697	968
124	760	995	593	932
150	786	995	772	1182
174	662	1001	645	962
212	674	953	627	950
294	684	898	696	1180
380	742	986	645	1099
Mean±SD	706±53	1008±79	680±66	1038±104

responses from adult muscles also indicated no significant difference between *Swl* and normal muscles although the scatter of responses obtained from the *Swl* muscles appeared to be larger than normal (fig. 3c, d). The mean strength of tetanic responses from normal soleus and EDL were 1.66±0.18 g/mg (n = 10) and 2.1±0.2 g/mg (n = 10), respectively, and those for *Swl* soleus and EDL were 1.53±0.34 g/mg (n = 12) and 2.02±0.33 g/mg (n = 12) (soleus $P > 0.1$; EDL $P > 0.05$). Stimulation of the nerve to the muscles resulted in mechanical responses, the amplitude of which was always close to that obtained by direct stimulation as expressed in fig. 4.

The twitch responses to direct stimulation showed that *Swl* soleus and EDL had developed characteristics similar to normal muscles (fig. 5). *Swl* soleus was clearly a slow-twitch muscle and *Swl* EDL was fast-twitch. However, closer examination of the values obtained showed that soleus had become slightly faster and EDL slightly slower, the rise and half relaxation times of *Swl* EDL are significantly different from normal ($P < 0.05$ for rise time; $P < 0.01$ for half relaxation time, paired t test). The rise time of *Swl* soleus was significantly different from the normal ($P < 0.05$) but the half relaxation time was not. The mean value of *Swl* half relaxation time was lower than that of normal (65±7 ms, n = 10; and 71±8 ms, n = 10, respectively) but this difference was not significant, $P > 0.1$ (Table 2). The small but significant changes in the twitch characteristics of *Swl* soleus and EDL were not accompanied by any change in the fatigue index of the muscles (Table 2).

Twitch responses to increasing strength of indirect stimulation allowed an estimation of the number of motor units present in adult soleus and EDL by the incremental steps in the mechanical response as motor units were recruited. This method tends to underestimate the number of motor units since several motor axons may have the same or very similar excitabilities and small motor units may be difficult to distinguish within

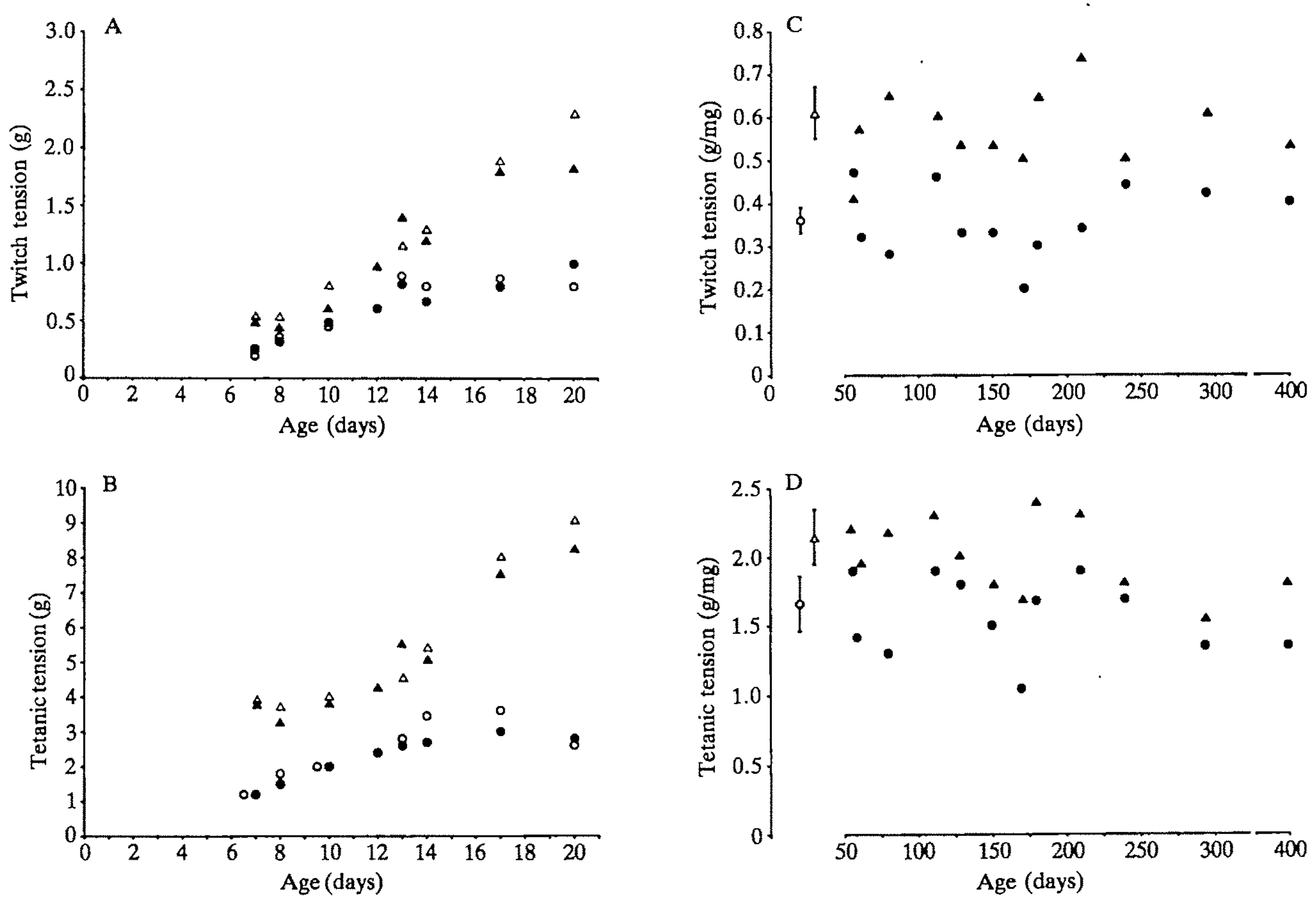

FIG. 3. Development of maximal twitch and tetanic tension to direct stimulation of normal soleus (open circles), normal EDL (open triangles), *Swl* soleus (filled circles) and *Swl* EDL (filled triangles). A, days 7–20, twitch responses to 100 V, 0.5 ms, 1 Hz. B, days 7–20, tetanic stimulation (parameters as in A) of soleus muscles at 20 Hz and EDL at 45 Hz. C, days 50–400, twitch responses expressed as g tension per mg muscle weight. Mean ± SD of normal soleus, 0.35 ± 0.02 (n = 10); normal EDL, 0.61 ± 0.06 (n = 10). D, days 50–400, tetanic responses expressed as g tension per mg muscle wt. Mean ± SD of normal soleus, 1.2 ± 0.1 (n = 10); normal EDL, 1.5 ± 0.1 (n = 10).

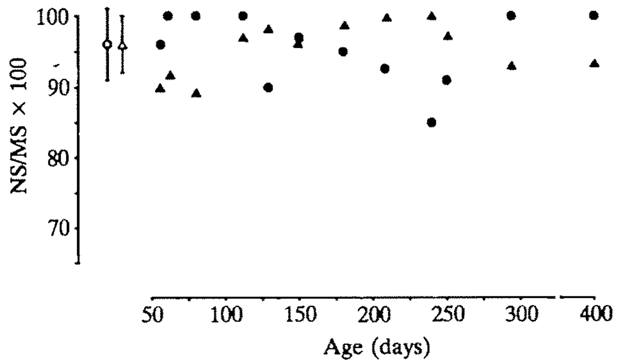

FIG. 4. Tetanic tension developed by normal soleus (open circle), normal EDL (open triangle), *Swl* soleus (filled circles) and *Swl* EDL (filled triangles) to supramaximal indirect stimulation. Results shown are the tension to indirect stimulation (NS) expressed as a percentage of that developed to direct stimulation (MS). Mean ± SD of normal soleus, 97 ± 4% (n = 10); normal EDL, 97 ± 3% (n = 10).

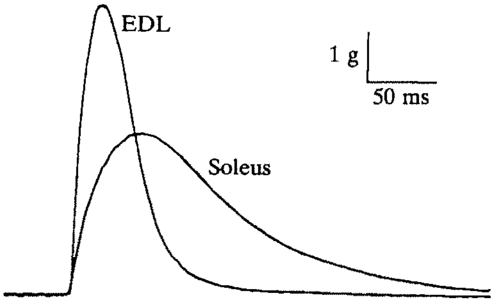

FIG. 5. Maximal twitch responses to direct stimulation of *Swl* EDL and soleus. Each response averaged from 5 consecutive sweeps. EDL and soleus are clearly distinguishable as fast and slow-twitch muscles.

the gross mechanical response. In both normal and *Swl* mice, EDL was found to have more motor units than soleus. Adult *Swl* and normal soleus were found to have 20–25 motor units, whereas *Swl* and normal EDL had 30–38 motor units.

It is of interest that stimulation of the whole nerve to EDL initially led to an underestimate of the number of motor units. The nerve to EDL bifurcates just before it enters the muscle and the separation and stimulation of each branch led to the detection of a larger number of motor units. The loss of afferent input appears to have had little effect on motor unit survival in either muscle (Table 3).

Electrophysiology

The calculated mean resting membrane potentials of both *Swl* soleus and EDL muscle fibres were all within the limits of normal. Estimates from fibres of adult normal soleus and *Swl* soleus muscles were 72.6 ± 5 mV (310 fibres, 10 muscles) and 72.8 ± 3 mV (380 fibres, 12 muscles), respectively, and the values for normal and *Swl* EDL were 80.5 ± 5 mV (316 fibres, 10 muscles) and 80.3 ± 4 mV (389 fibres, 12 muscles), respectively.

At all end-plates sampled spontaneous MEPPs and evoked EPPs could be seen. The MEPP amplitudes recorded from *Swl* muscles were in the normal range. There was a small but significant reduction in the frequency of MEPP release at *Swl* EDL motor end-plates ($P < 0.05$). The frequencies recorded from *Swl* EDL varied from 0.36 to 3.0/s which is a larger range than that recorded from normal EDL end-plates (range

TABLE 2. CONTRACTILE CHARACTERISTICS OF SOLEUS AND EXTENSOR DIGITORUM LONGUS OF NORMAL AND *Swl* MICE

	Normal soleus			*Swl soleus*		
Age (days)	*Rise time (ms)*	*Half relaxation time (ms)*	*Fatigue index (%)*	*Rise time (ms)*	*Half relaxation time (ms)*	*Fatigue index (%)*
56	60	87	85	42	60	95
61	62	85	80	60	62	90
80	58	70	88	50	68	83
112	40	60	89	40	60	84
129	58	69	92	60	70	95
150	55	70	90	60	80	90
171	50	65	95	45	58	80
240	60	69	95	50	70	85
294	62	70	100	58	70	90
382	57	68	89	45	57	95
Mean ± SD	56 ± 7	71 ± 8	90 ± 6	51 ± 8	65 ± 7	87 ± 5

	Normal EDL			*Swl EDL*		
Age (days)	*Rise time (ms)*	*Half relaxation time (ms)*	*Fatigue index (%)*	*Rise time (ms)*	*Half relaxation time (ms)*	*Fatigue index (%)*
56	20	19	60	24	18	60
61	17	17	50	20	28	35
80	19	15	45	19	14	45
112	19	20	50	19	20	51
129	20	20	52	23	22	42
150	20	16	45	25	24	42
171	21	20	55	22	24	56
240	19	21	50	24	31	45
294	21	21	45	20	27	65
382	21	20	52	21	23	45
Mean ± SD	19.7 ± 1	18.9 ± 1	50 ± 5	21.7 ± 2	23.1 ± 4	49 ± 9

TABLE 3. NUMBER OF MOTOR UNITS IN SOLEUS AND EXTENSOR DIGITORUM LONGUS OF NORMAL AND *Swl* MICE

Age (days)	*Normal soleus*	*Swl soleus*	*Normal EDL*	*Swl EDL*
7	10	10	12	12
8	10	9	13	14
10	12	13	15	15
13	24	17	19	19
14	17	23	21	26
17	18	19	25	28
20	19	20	30	32
56	20	21	30	32
61	20	15	36	35
80	21	17	34	34
112	21	19	32	33
129	22	21	35	34
150	19	21	34	36
171	21	25	33	38
240	22	16	35	35
294	21	20	36	37
382	21	20	33	33

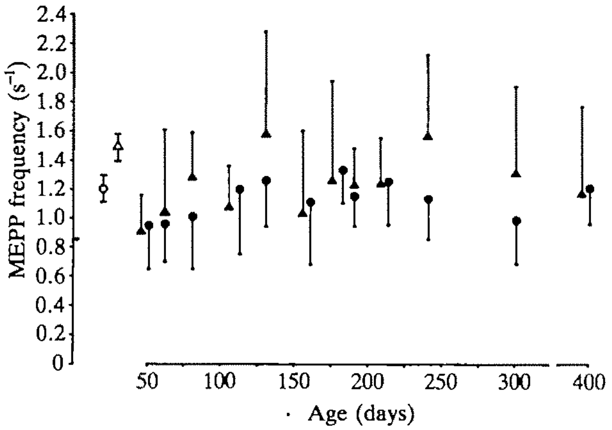

FIG. 6. Miniature end-plate potential (MEPP) frequency of normal soleus (open circle), normal EDL (open triangle), *Swl* soleus (filled circles) and *Swl* EDL (filled triangles) muscles. Symbols for *Swl* muscles represent the mean ± 1 SD of at least 30 fibres from each muscle. Mean ± SD of normal soleus, 1.2 ± 0.1/s (325 fibres, 10 muscles); normal EDL, 1.5 ± 0.1/s (340 fibres, 10 muscles).

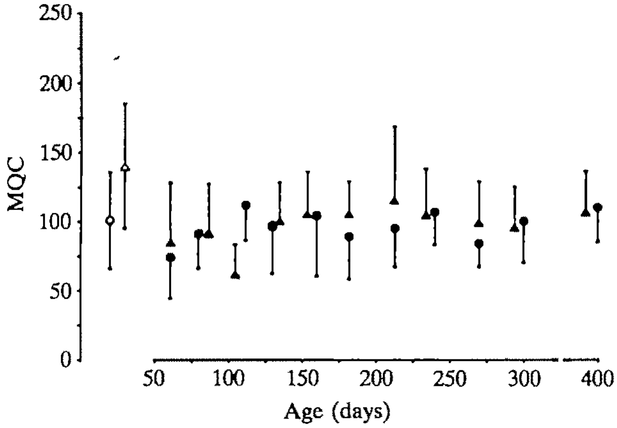

FIG. 7. Mean quantal content (MQC) of end-plate potentials from normal soleus (open circle), normal EDL (open triangle), *Swl* soleus (filled circles) and *Swl* EDL (filled triangles). Values calculated by the method of variance. Symbols for *Swl* muscles represent mean ± 1 SD derived from at least 15 fibres in each muscle. Mean ± SD of normal soleus, 101 ± 35 (165 fibres, 10 muscles); normal EDL, 136 ± 45 (157 fibres, 10 muscles). The MQC of *Swl* is consistently lower than normal.

0.9–2.0/s). This marked variability in the values obtained from *Swl* EDL end-plates is reflected in the unusually large SDs shown in fig. 6. MEPP frequencies recorded from *Swl* soleus showed no difference from the normal.

It was found that in *Swl* EDL the MQC of end-plate potentials was abnormally low (fig. 7). Under identical conditions, EPPs in normal EDL showed a significantly higher MQC (136 ± 45; n = 10) than soleus end-plates (101 ± 35; n = 10). However, values obtained for *Swl* EDL were significantly lower than normal ($P < 0.01$). They did not show the expected difference from soleus end-plates, either from normal or *Swl* animals. In some instances the MQC of *Swl* EDL was actually below that of the soleus removed from the same animal. In no instance was there a decrement in EPP amplitude during prolonged stimulation.

The nerve to each muscle was only a few mm in length and it was not possible to obtain meaningful values of the conduction velocity of propagated impulses. However, it was clear that there was no difference in the latency of the evoked responses from *Swl* muscles when compared with those of the normal. Estimates of means of normal and *Swl* EPP latencies recorded from soleus were 1.23±0.1 ms (n = 10) and 1.18±0.1 ms (n = 12), respectively, and those for normal and *Swl* EDL were 1.16±0.1 ms (n = 10) and 1.09±0.1 ms (n = 12), respectively.

Muscle fibre histochemistry

Muscle fibres were classified according to Brooke and Kaiser (1970). Despite the faster than normal twitch characteristics of *Swl* soleus and the slower characteristics shown by *Swl* EDL, both muscles exhibited normal staining patterns for myosin ATPase and mitochondrial oxidative enzyme activity. Soleus muscles were composed of type I and type IIA muscle fibres in roughly equal proportions, both types rich in mitochondrial oxidative enzyme activity. Almost all the muscle fibres of EDL were type II, approximately 50% were rich in mitochondrial oxidative enzyme activity (type IIA) and the remainder (type IIB) possessed very little oxidative enzyme activity. Occasionally there were a few type I muscle fibres scattered throughout EDL.

The diameters of histochemically identified muscle fibres were measured on the Kontron image analyser and the grouped results are shown in Table 4. It was apparent that in soleus, both type I and type IIA fibres had mean diameters of approximately 40 μm. However, the fibre diameters measured in EDL showed marked differences between fibre types. Type IIB muscle fibres were the largest (approximately 53 μm), type IIA were intermediate in size (approximately 33 μm) and type I the smallest (approximately 28 μm). Type I and type IIA muscle fibres in EDL have smaller mean diameters than type I and type IIA fibres in soleus. This seems an unexpected observation but may relate to the fact that motor units of the same histochemical profile but situated in a different muscle may differ in their physiological characteristics (Burke *et al.*, 1973, 1974). There were no observable differences in the distribution of fibre diameters in *Swl* muscles compared with the normal. In particular, the large diameter (type IIB) fibre component in EDL was present in similar proportion to the normal. This is of relevance to the findings in relation to measured end-plate areas.

TABLE 4. DIAMETER OF MUSCLE FIBRES IN SOLEUS AND EXTENSOR DIGITORUM LONGUS OF NORMAL AND *Swl* MICE*

Fibre type	*Normal EDL*	*Swl EDL*	*Normal soleus*	*Swl soleus*
Type I	28±4 (5, 120)	30±4 (5, 152)	42±5 (5, 949)	42±6 (5, 980)
Type IIA	33±7 (5, 842)	36±8 (5, 943)	42±6 (5, 965)	41±5 (5, 938)
Type IIB	53±6 (5, 895)	52±7 (5, 885)		

* Fibre diameters (in μm) are expressed as mean±SD. The first figure in parentheses represents the number of muscles studied, the second the total number of muscle fibres measured.

End-plate areas

The end-plates in muscles of adult mice were stained with BIA and the areas measured on the image analyser. Only end-plates which were viewed 'en-face' were sampled. The results are shown in fig. 8.

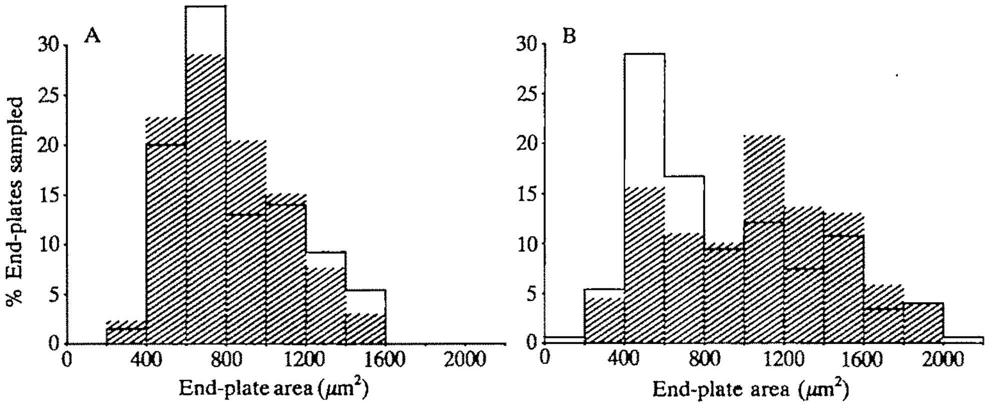

FIG. 8. Area of end-plates from *Swl* (open columns) and normal (hatched columns) muscles stained with bromoindoxyl acetate. In soleus (A) the size distribution of *Swl* end-plates is within normal limits. In EDL (B) *Swl* shows a deficiency in large end-plates.

Areas of end-plates in EDL of normal mice showed a bimodal distribution with the peaks appearing at 400–600 μm^2 and 1000–1200 μm^2; the mean end-plate area being 1049±417 μm^2 (n = 154). Control soleus end-plate areas showed a unimodal distribution about a peak at 600–800 μm^2. The mean end-plate area was 813±267 μm^2 (n = 132). It is probable that the distribution of end-plate areas in normal EDL and soleus reflects the distribution of muscle fibre diameters found in these muscles. Kuno *et al.* (1971) and Harris and Ribchester (1979) have shown that there is a strong correlation between muscle fibre diameter and end-plate area. The distribution of end-plate areas in *Swl* soleus showed no significant difference from normals. The unimodal peak occurred at 600–800 μm^2 with a mean area of 838±297 μm^2 (n = 130).

The distribution of motor end-plate areas in *Swl* EDL showed only a single peak at 400–600 μm^2 thus differing markedly from the normal. Many more end-plates than normal fell within the 400–600 μm^2 range apparently at the expense of the 1000–1200 μm^2 peak. The mean end-plate area in these muscles was 907±440 μm^2 (n = 147), a substantial shift towards a smaller size. In view of the finding of a normal fibre diameter distribution in *Swl* EDL muscles the implication is that many large diameter muscle fibres are innervated at end-plates that are smaller than would be expected.

Paraffin histology

A striking feature of *Swl* muscles was the appearance of marked swelling of axons just proximal to many end-plates. The silver impregnation for axons was carried out on sections of muscles from animals 2–6 months of age. The degree of swelling was quite variable but affected nerve fibres were clearly distended and readily distinguishable from normal. There were no signs of axonal degeneration associated with the swollen axons. Not all motor axons appeared swollen and it was not uncommon to see grossly distended axons near to axons of normal thickness (fig. 9).

Electron microscopy

An extensive morphometric study of the ultrastructure of motor end-plates from *Swl* and normal muscles was undertaken. The parameters investigated by morphometry can be defined as follows. The *axon terminal area* seen in electron micrographs is the area of terminal axoplasm contained within the axolemmal membrane, and the *end-plate area* is the area of muscle fibre delineated by a line drawn to contain all postsynaptic folds; the *presynaptic length* is the length of axolemmal membrane apposed to postjunctional sarcolemmal membrane, and the *postsynaptic length* is the length of sarcolemmal membrane measured within the defined end-plate area. The results are shown in Tables 5 and 6.

It was apparent that there were differences in axon terminal area between soleus and EDL of normal mice, the mean axon terminal area in soleus being substantially larger than those in EDL. In *Swl* end-plates the areas of terminals of soleus and EDL were different from the normal. The mean axon terminal area of *Swl* soleus was smaller than normal and the mean axon terminal area of *Swl* EDL was larger than normal.

The most striking differences observed were in the postsynaptic specializations of the sarcolemmal membrane of *Swl* EDL. There was a significant reduction in the amount of secondary postsynaptic specialization at the *Swl* neuromuscular junction shown by the reducd postsynaptic membrane length in relation to terminal area and presynaptic length ($P < 0.001$, Kruskal-Wallis one way analysis of variance). Morphological differences between end-plates of normal red, white and intermediate muscle fibres included differences in the length and complexity of the secondary postsynaptic folds (Padykula and Gauthier, 1970; Duchen, 1971; Santa and Engel, 1973). The end-plates of fast-twitch (white) muscle fibres were reported to have significantly more and deeper secondary postsynaptic folds than those of slow-twitch (red) or intermediate muscle fibres. The morphometric analysis of normal soleus and EDL end-plates reported here confirm this observation. In the *Swl* EDL end-plates, the ratio of postsynaptic length to presynaptic length, and the ratios of postsynaptic length and end-plate area to axon terminal area all showed highly significant reductions, shifting figures towards values expected of soleus end-plates.

Vesicle density was significantly higher in normal soleus motor nerve terminals than in the *Swl* nerve terminals, although estimates of MQC showed no difference between the two groups. On the other hand in EDL vesicle density in normal and *Swl* terminals showed no significant difference whilst physiologically there was a marked reduction in the MQC at *Swl* nerve terminals. This suggests that the concentration of vesicles alone does not reflect the amount of transmitter released from nerve terminals. A similar conclusion concerning the relationship of vesicle density to transmitter release was drawn by Banker *et al.* (1983) when comparing motor end-plates from young and aged mice.

There were other trends revealed by the morphometric analysis which did not reach the statistically highly significant level of 0.1% but were significant at the 5% level. *Swl* EDL motor nerve terminals contained more mitochondria than normal but this was not seen in *Swl* soleus nerve terminals. By electron microscopy many swollen preterminal

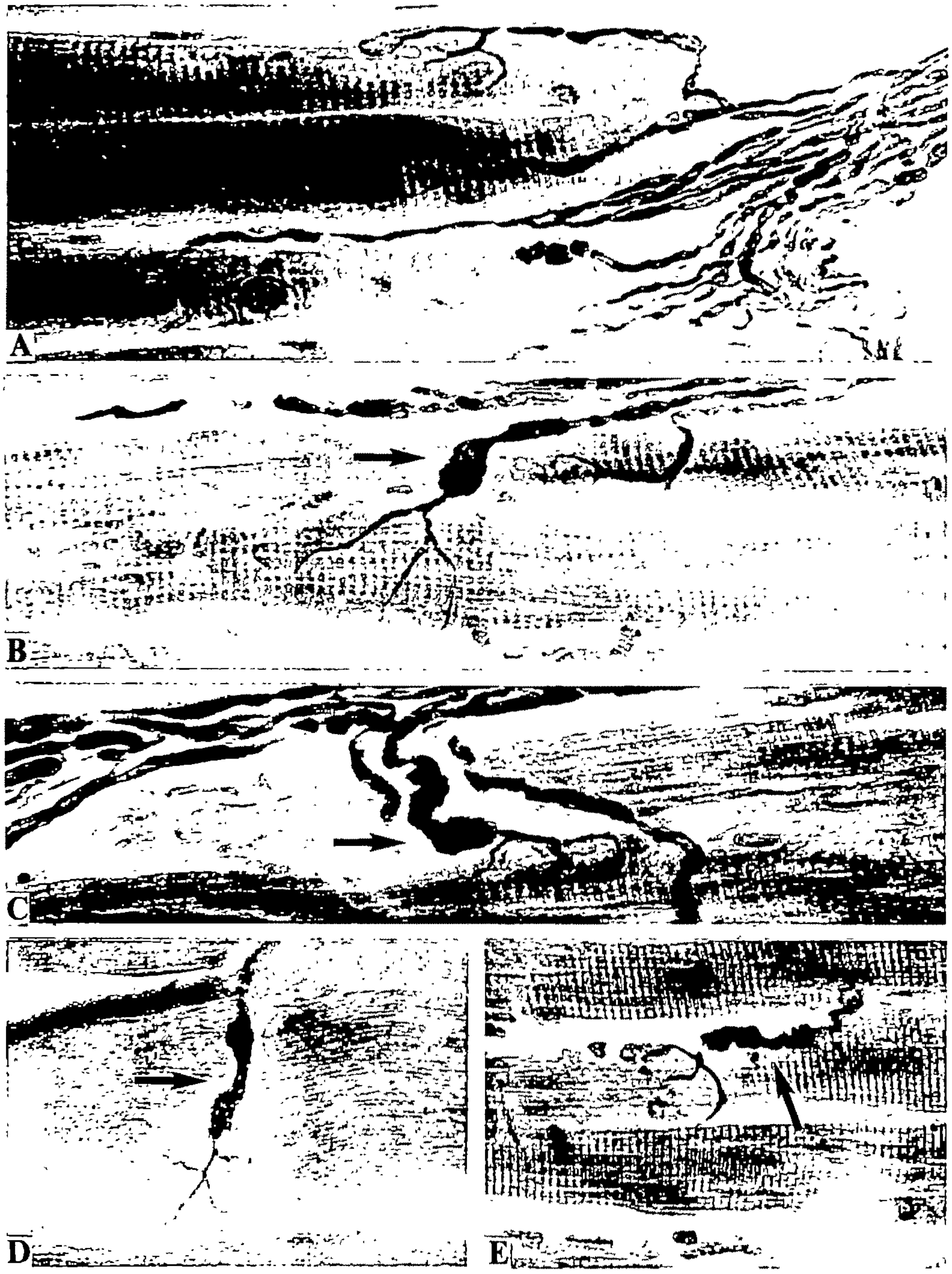

FIG. 9. Longitudinal paraffin sections of muscles of *Swl* mice showing preterminal axons and terminal arborizations. The pattern of innervation of *Swl* muscles is normal and there is no excessive preterminal axonal branching or terminal axonal sprouting. In A the appearances are within normal limits; in B – E there are swellings (arrows) of preterminal axons. Glees silver impregnation ×600.

TABLE 5. MORPHOMETRIC ANALYSIS OF NEUROMUSCULAR JUNCTIONS (NMJ) IN SOLEUS OF NORMAL AND *Swl* MICE

	Control soleus	*Swl soleus*
Number of NMJ	57	40
Axon terminal area (μm^2)	6.2 ± 3.3	5.4 ± 3.4**
End-plate area (μm^2)	4.8 ± 2.9	4.3 ± 1.9
End-plate area/axon terminal area	0.9 ± 0.7	1.1 ± 0.9
Presynaptic length (μm)	6.7 ± 2.8	5.5 ± 1.8
Postsynaptic length (μm)	29 ± 16	23 ± 12
Area of axon terminal occupied by mitochondria (%)	15.1 ± 9.6	14.1 ± 9.6
Postsynaptic length/axon terminal area ($\mu m/\mu m^2$)	5.6 ± 3.9	6.4 ± 5.9
Postsynaptic fold density ($\mu m/\mu m^2$)	6.4 ± 1.9	5.6 ± 1.4
Post/presynaptic length	4.2 ± 1.8	4.3 ± 2.0
Vesicle density (per μm^2)	64 ± 18	49 ± 23**

* All results expressed as mean ± SD. ** $P < 0.001$ (Kruskal-Wallis test).

TABLE 6. MORPHOMETRIC ANALYSIS OF NEUROMUSCULAR JUNCTIONS (NMJ) IN EXTENSOR DIGITORUM LONGUS OF NORMAL AND *Swl* MICE

	Control EDL	*Swl EDL*
Number of NMJ	49	59
Axon terminal area (μm^2)	3.9 ± 2.3	5.1 ± 3.6**
End-plate area (μm^2)	5.2 ± 2.8	4.7 ± 3.3
End-plate area/axon terminal area	2.1 ± 2.4	1.1 ± 0.8**
Presynaptic length (μm)	5.3 ± 2.2	5.4 ± 2.6
Postsynaptic length (μm)	33.2 ± 15	27 ± 16
Area of axon terminal occupied by mitochondria (%)	11.4 ± 8.6	15.1 ± 8.3
Postsynaptic length/axon terminal area ($\mu m/\mu m^2$)	13.5 ± 16.1	6.7 ± 4.8**
Postsynaptic fold density ($\mu m/\mu m^2$)	6.5 ± 1.0	6.4 ± 1.7
Post/presynaptic length	7.3 ± 5.2	5.4 ± 3.5**
Vesicle density (per μm^2)	53 ± 21	49 ± 19

* All results expressed as mean ± SD. ** $P < 0.001$ (Kruskal-Wallis test).

axons were found, these being the ultrastructural equivalent of the argyrophilic axonal swellings seen in the paraffin sections of both *Swl* soleus and EDL. These swellings were situated in the last internode, around which the myelin sheath appeared abnormally thin (fig. 10) or in the unmyelinated axon distal to the last heminode. The axoplasm was densely packed with neurofilaments haphazardly arranged and lacking the normal orientation in the long axis of the axon (fig. 11). At some end-plates the axonal terminals were also greatly distended by neurofilaments which occupied most of the terminal, leaving only a few clusters of vesicles close to the presynaptic axonal membrane (fig. 12). There was no evidence of axonal degeneration on electron microscopy and

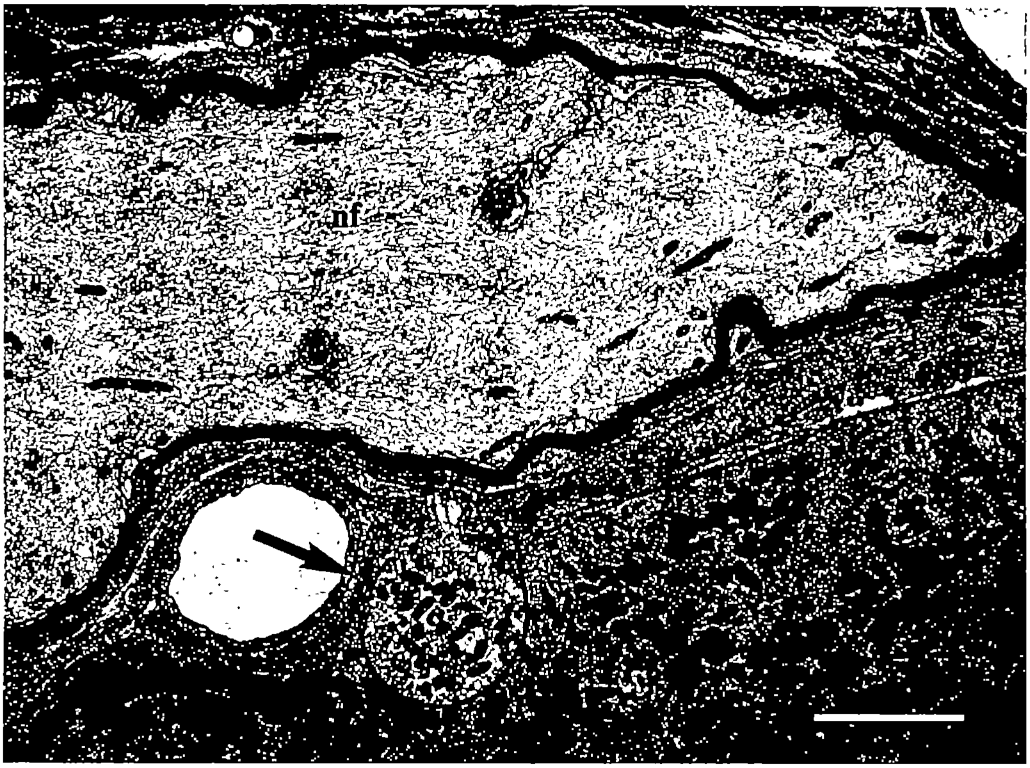

FIG. 10. Electron micrograph showing preterminal internode of motor axon in *Swl* soleus. The axon is markedly swollen and packed with neurofilaments (nf). This axon was shown by serial sections to innervate the end-plate, part of which is shown (arrow). Bar = 3 μm.

at no end-plate was there bared postsynaptic membrane suggesting denervation, in keeping with the absence of any electrophysiological evidence of denervation.

There were no axonal accumulations of neurofilaments in roots or peripheral nerves. Some sensory ganglion cells have been reported to contain excessive numbers of neurofilaments (Duchen and Scaravilli, 1977*b*), as is also seen in chromatolytic neurons.

DISCUSSION

The normal development of muscle is dependent on its innervation (Engel and Karpati, 1968) and the differentiation of muscle fibre characteristics is largely dependent on the properties of the motoneurons innervating them (Buller *et al.*, 1960; Close, 1964).

Corner and Schadé (1967) suggested that electrical activity may play an important role in the development of nerve cells. Nelson and Mendell (1979) and Nelson *et al.* (1979) found long lasting increases in the amplitude of excitatory postsynaptic potentials in partially deafferented neurons. Bernstein and Bernstein (1973) observed shrinkage of the dendritic arborization of deafferented motoneurons whilst Kjerulf *et al.* (1973)

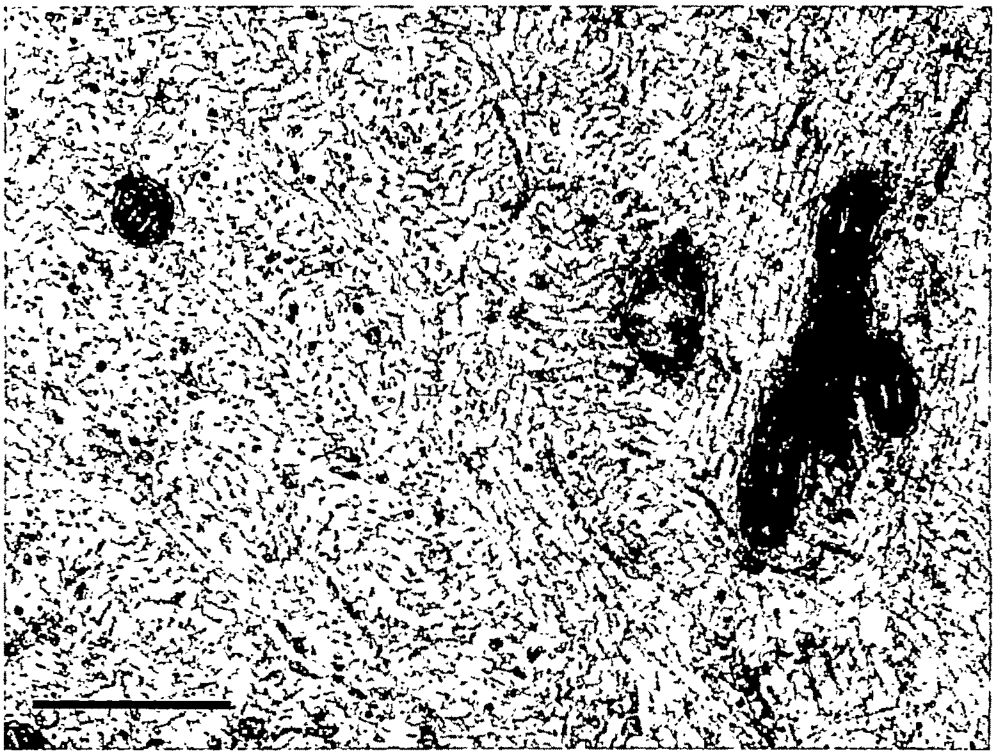

FIG. 11. Axoplasm from a swollen preterminal axon in *Swl* soleus is packed with neurofilaments (approximately 10 nm diameter) which are haphazardly orientated. Bar = 0.5 μm.

reported a marked reduction in the number of dendritic spines of deafferented cuneate neurons which also showed spontaneous hyperactivity. Gustafsson *et al.* (1982) studied membrane characteristics of partially deafferented spinal motoneurons and found a reduction in the membrane time constant as well as an increase in input resistance. Some of the changes in motoneurons lasted only a matter of days, others lasted several months. In *Swl* mice, the loss of proprioceptive innervation at an early stage of development may have led to abnormalities in motoneuron structure and function. This possibility is emphasized by the fact that during normal development muscle spindles and tendon organs are present and functional at an early stage and that a monosynaptic reflex can be demonstrated as early as day 19 of gestation (Zelená, 1964; Saito, 1979).

Polyneuronal innervation

Polyneuronal innervation of mammalian skeletal muscle and its elimination during the first few postnatal weeks was first reported by Redfern (1970). The mechanisms controlling the elimination of synapses at the neuromuscular junction are not well understood. It seems that the level of neuromuscular activity plays an important role

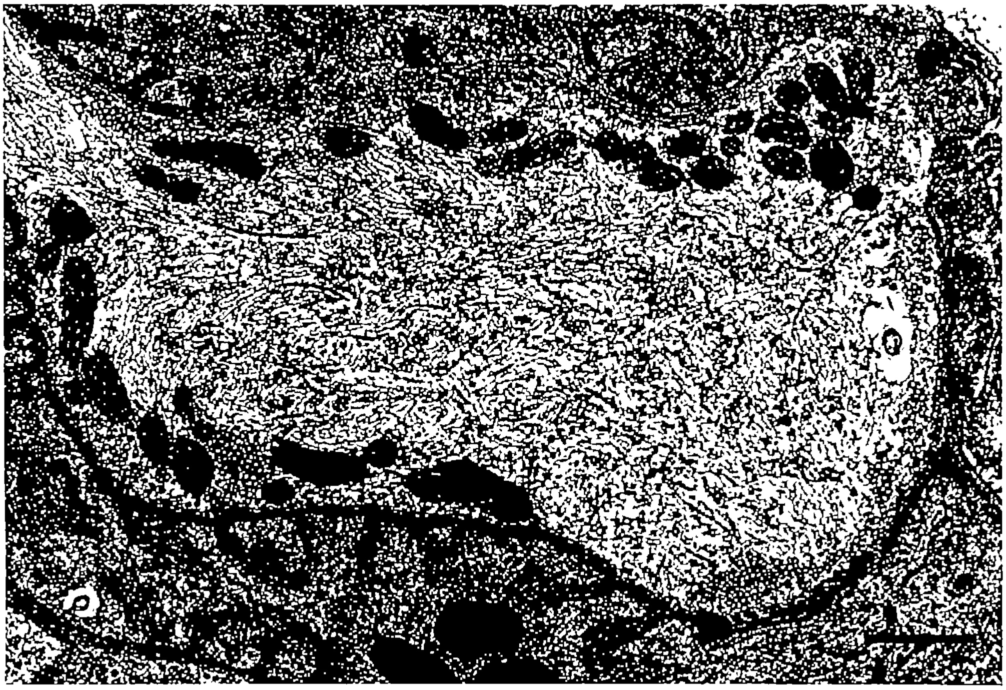

FIG. 12. Motor end-plate in *Swl* soleus showing an axonal terminal rather swollen and packed with neurofilaments. Synaptic vesicles are few in number and lie in clusters close to the presynaptic axolemma. There is no evidence of degeneration or of denervation of the postsynaptic membrane. Bar = 3 μm.

in newborn animals. Reduction of activity by surgical or pharmacological methods has been reported to delay the elimination of polyneuronal innervation (Benoit and Changeux, 1975; Riley, 1978; Srihari and Vrbová, 1978; Thompson *et al.*, 1979; Zelená *et al.*, 1979; Miyata and Yoshioka, 1980; Caldwell and Ridge, 1983). Conversely, increased activity brought about by electrical stimulation of the sciatic nerve is reported to hasten synapse elimination (O'Brien *et al.*, 1978).

Redfern (1970) suggested that the afferent input to spinal motoneurons from muscles may play a role in determining the rate at which excess neuronal innervation was removed. However, Caldwell and Ridge (1983) reported that dorsal root transection in 7 day old rats had no effect on the rate of elimination of polyneuronal innervation. The results reported in the present paper support this observation, physiological and morphological observations both showing a similar timing of synapse elimination in *Swl* and normal muscles.

The role of a postnatal increase in the number of muscle fibres in synapse elimination appears to be unresolved (*see* Balice-Gordon and Thompson, 1988). Rowe and Goldspink (1969) and Habgood *et al.* (1984) showed that adult mouse soleus was composed of approximately 700 and EDL of approximately 1000 muscle fibres. Our results are in agreement with these numbers and indicate that there was little or no postnatal addition of muscle fibres in either normal or *Swl* muscles. Therefore the rate of elimination of synapses was not influenced by changes in the number of muscle fibres. Similar findings were made in rat EDL (Ontell and Dunn, 1978; Balice-Gordon and Thompson, 1988) and rabbit soleus (Bixby and Van Essen, 1979). On the other hand Betz *et al.* (1979) reported that the number of muscle fibres in rat lumbrical muscles almost doubles during the first few days after birth. It seems that the lumbricals are less developed than soleus and EDL at birth. The postnatal addition of muscle fibres may therefore contribute to synapse elimination in some muscles.

Neuromuscular junction and transmission

The most striking abnormality revealed by the electrophysiological recordings was that the parameters of MEPP frequency and MQC of *Swl* EDL motor end-plates were indistinguishable from those of either normal or *Swl* soleus. Normally the nerve terminals of motoneurons innervating EDL release more neurotransmitter (as measured by the mean quantal content) than do those innervating soleus. The frequency of the spontaneous release of MEPPs is also characteristically higher at end-plates of fast-twitch than of slow-twitch muscles in the mouse (Duchen and Tonge, 1973).

The strong correlation between end-plate size and the quantal content of the EPP has been reported by Kuno *et al.* (1971) and Harris and Ribchester (1979). It is interesting to note that in *Swl* EDL the MQC and MEPP frequency, together with the size of the end-plates, were all significantly smaller than normal.

There is known to be a strong correlation between muscle fibre diameter and end-plate size (*see* Bowden and Duchen, 1976). This correlation does not appear to hold in *Swl* EDL. The smaller than normal end-plate area in *Swl* EDL was not associated with a reduction in fibre diameter. An investigation similar to that of Harris and Ribchester (1979) in which end-plate areas were measured in dissociated muscle in which fibre diameter could easily be measured, would be required to show conclusively that the large diameter muscle fibres had abnormally small end-plates. However, the method used in our investigation was successful in showing the bimodal distribution in end-plate size in the normal so that it seems unlikely that our findings in *Swl* EDL were due to technical or sampling errors. It seems that the physiological and morphological characteristics of neuromuscular transmission in *Swl* EDL have become more like those of soleus.

Ultrastructural analysis also showed that *Swl* EDL exhibited trends towards soleus in respect of the postsynaptic specialization. The size of end-plate area (here meaning the area of sarcoplasm occupied by the postsynaptic folds) and the amount of postsynaptic specialization are parameters which are characteristically greater at end-plates of fast than slow fibres (Padykula and Gauthier, 1970; Duchen, 1971; Santa and Engel, 1973). The highly significant reductions in all these parameters suggest that the ultrastructural end-plate characteristics in *Swl* EDL had shifted away from those typical of a fast-twitch towards those of a slow-twitch muscle.

Terminals in *Swl* soleus tended to be smaller than normal while those of *Swl* EDL were larger than normal. Since in normal controls, in keeping with the observations of Santa and Engel (1973), the soleus terminals were larger than those in EDL, the trend in *Swl* seems to be towards less obvious differentiation between fast and slow terminals.

The accumulations of neurofilaments in the axoplasm of preterminal motor nerve fibres caused marked axonal swelling and thinning of the myelin sheath of the last internode. Accumulation of neurofilaments in the axonal terminals were present in a small proportion of end-plates. These abnormalities are comparable in many respects with those caused by acrylamide intoxication (*see* Jacobs and Le Quesne, 1984) which causes focal accumulation of neurofilaments particularly affecting the distal parts of long axons. Degeneration is found in acrylamide neuropathy but not in *Swl* nerves or nerve terminals. Accumulation of neurofilaments in motor nerve endings in acrylamide neuropathy was described by Prineas (1969) and Tsujihata *et al.* (1974). This was associated with depletion of synaptic vesicles and partial denervation of the postsynaptic membrane. As in the axonal swellings of the *Swl* nerves, the neurofilaments were randomly arranged and lacked the normal orientation in the long axis of the nerve fibre. A decrease in the frequency of MEPPs and in the pool of transmitter available for release was also reported by Tsujihata *et al.* (1974), changes which were also observed at *Swl* end-plates. Souyri *et al.* (1981) reported that acrylamide toxicity was associated with the accumulation of fast-transported proteins in the preterminal regions of axons. It may be that in *Swl*, although there was no degeneration of terminals, some impairment of axonal transport may be responsible for the failure of large motoneurons to maintain the expected large end-plates on type IIB muscle fibres.

Number of motor units

Swl soleus and EDL developed normal numbers of motor units. The values estimated for soleus were in the range previously reported for mouse soleus. The numbers have been estimated to be between 20 and 28 (Law and Caccia, 1975; Lewis *et al.*, 1982; Parry *et al.*, 1982; Habgood *et al.*, 1984).

It was found that the number of motor units in normal or *Swl* EDL (30–38) did not agree with that reported by Bateson and Parry (1983) who estimated approximately 20 motor units in normal and dystrophic EDL muscles. The technique employed by Bateson and Parry was to measure the amplitude of 4 single motor units in each muscle, isolated by splitting ventral root filaments and to divide the total twitch amplitude by the mean of these 4 units. The method used by Bateson and Parry (1983) requires the assumption that the motor units recorded are representative of all those within the muscle; this may not have been the case. Observations made by other workers on the size distribution of motor units in a mixed fast twitch muscle have reported a wide range of motor unit tensions (Burke, 1967; Burke *et al.*, 1973). In the present investigation the number of motor units in soleus and EDL of *Swl* were closely similar to those in normal muscles. Removal of afferent input to motoneurons of the developing frog and chick has been reported to lead to a marked but variable reduction in the number of surviving motoneurons by Davis *et al.* (1983) and Okado and Oppenheim (1984), whose results suggest that afferent as well as efferent connections (Pittman and Oppenheim, 1979) are necessary for the survival of spinal motoneurons during development. It was suggested that the variability of the results was due to compensatory sprouting from remaining afferents allowing partially deafferented motoneurons to survive. The normal numbers of motor units in both soleus and EDL of *Swl* mice suggests that compensatory sprouting of remaining afferents may have occurred following ganglion cell death during fetal development.

Mechanical responses

It was found that the development of twitch and tetanic tension and fatigability in *Swl* muscles was unaffected. The rate of development of both characteristics closely matched those of normal muscles. Muscle fibre diameters and the staining characteristics as revealed by enzyme histochemistry were also normal, suggesting that *Swl* muscles are not subjected to marked hypoactivity or hyperactivity as a consequence of reduced afferent influence on spinal motoneurons. Deafferentation of normal adult muscles by section of dorsal roots has no effect on the strength of mechanical responses or on muscle fibre diameters (Tower, 1931; Buller and Pope, 1977). That fetal and neonatal muscles lacking proprioceptive feedback are capable of apparently normal development is a new observation.

The only mechanical responses of *Swl* muscles which were abnormal were their twitch characteristics. Although *Swl* soleus was clearly a slow twitch and EDL a fast twitch muscle, there were significant alterations in the rise and half relaxation times compared with normal. These findings are similar to those of Buller *et al.* (1960) who showed that the development of twitch characteristics of slow muscle was dependent on motor nerve activity but the development of fast twitch characteristics was relatively independent of nerve activity. It is possible that the lack of proprioceptive feedback from an early stage leads to minor alterations in the firing rates of fast and slow motoneurons or to alterations in the trophic relationship between the nerve and muscle.

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RELEASE OF COLD-INDUCED BURNING PAIN BY BLOCK OF COLD-SPECIFIC AFFERENT INPUT

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SUMMARY

While the pure sensation of cold is evoked by activation of a specific set of afferent channels, an additional set is believed to be activated by noxious low-temperature stimuli evoking cold pain. At primary afferent level, the channels concerned with the cold fraction of cold pain are served by myelinated A delta cold-specific fibres, whereas those concerned with the pain fraction are served by unmyelinated C nociceptors. In the present study, interaction between the two types of afferent input underlying cold pain was investigated by selectively blocking conduction in myelinated fibres. When doing so to the point of abolishing cold sensation, ramps of low-temperature stimuli eventually evoked a first sensation of burning pain. In addition to, and contemporaneous with, this change in quality, a significant decrease in pain threshold (reduction in required stimulus energy) was recorded when applying a noxious low-temperature stimulus. Such exaggeration in magnitude of low temperature-induced pain and the unmasking of its burning quality by A fibre block imply release of central sensory transmission due to removal of inhibitory primary afferent input. Myelinated fibres transmitting either tactile, cold sensations or both could exert this inhibition. Previous evidence of suppression of pain by low-temperature stimuli indicates that it is the cold-specific input that normally exerts this central gating on nociceptor input. The present results may also offer an explanation for the occurrence of a syndrome of burning pain on cold exposure in neuropathic patients with impaired ability to perceive cold.

INTRODUCTION

Lowering skin temperature evokes a painless cold sensation which, on further reduction in temperature, becomes a cold and painful sensation: cold pain. Early thinking on sensory mechanisms interpreted pain from intense high or low temperature stimuli as simple upgrading in magnitude of warm or cold sensation due to increased afferent input (*see* Zotterman, 1972). Current thinking supports separate specific afferent channels as evoking thermal specific and thermal pain sensations. Indeed, there is now strong experimental and clinical support for the concepts that at primary afferent level (1) warm sensation is mediated by specific unmyelinated C fibres (Konietzny and Hensel, 1975; Hallin *et al.*, 1982); (2) cold sensation is mediated by small myelinated A delta fibres (Darian-Smith *et al.*, 1973; MacKenzie *et al.*, 1975; Adriaensen *et al.*, 1983); (3) heat-induced pain by unmyelinated polymodal nociceptors (Torebjörk, 1974; van Hees and Gybels, 1981), with participation, under certain circumstances, of small myelinated (A delta) nociceptors (LaMotte and Campbell, 1978); and (4) cold-induced pain by unmyelinated

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polymodal nociceptors (Torebjörk, 1974). It is thought that the cold quality of the pain induced by low temperature stimuli reflects coactivation of cold-specific A delta afferents (LaMotte and Thalhammer, 1982; Saumet *et al.*, 1985).

The advent of quantitative sensory testing techniques to measure psychophysical thresholds for warm, cold, heat pain and cold pain sensations (Fruhstorfer *et al.*, 1976; Lindblom and Verrillo, 1979; Claus *et al.*, 1987; Ziegler *et al.*, 1988) offers the opportunity to examine the detailed relationship between thermal specific and thermal pain submodalities under experimental conditions of dissociated nerve block. In doing so, through local compression-ischaemia, the present study not only confirms that low temperature-induced pain persists after abolition of cold sensation, but shows that its quality and magnitude are strikingly modified. Indeed, A fibre block of cold-specific input leads to an exaggeration of low temperature-induced pain, which becomes endowed with a burning quality.

These findings are a mirror image of those reported by Bini *et al.* (1984) who demonstrated rigorously how the application of cold stimuli elevates pain thresholds. While the overall observations support the general concept of gating in the central nervous system (Head, 1921; Noordenbos, 1959; Wall, 1978), in the clinical context they contribute to a better understanding of symptoms in certain patients with peripheral neuropathies, and further clarify mechanisms of cold-induced analgesia. Similar findings and equivalent conclusions have been reported recently through study of direct nerve compression, without ischaemia (Wahren *et al.*, 1989).

METHODS

Psychophysical thresholds

Subjective thresholds for cold sensation, warm sensation, cold-induced pain and heat-induced pain were measured during delivery of ramps of relatively low or high temperature stimuli using the Quantitative Thermotest (QTT) device (Somedic AB, Stockholm; Fruhstorfer *et al.*, 1976). A Peltier type thermode measuring 2.5×5 cm was applied to glabrous skin at and adjacent to the thenar eminence of normal human volunteers. The temperature of the thermode could either rise or fall, from the adapting temperature of 32° C, at various rates, depending on the direction and intensity of the current flow through the Peltier device. The temperature range of the probe was 5–50° C. The subject held a switch in the free hand, which was to be pressed at the *first sensation* of either warmth, cold, heat pain or cold pain. Pressing the switch reversed the temperature of the probe, returning it to the adapting level. An Omniscribe chart recorder (D 5000, Houston Instruments, Austin, Texas) registered temperature changes with time. The rates of temperature change were 2° C/s when detecting low temperature-induced sensation, and 4° C/s when detecting low temperature-induced pain. Such rates drop exponentially as stimulus temperature departs from baseline. An illustration of an actual record is given in fig. 1.

Compression-ischaemia nerve block

After obtaining baseline threshold measurements, a sphygmomanometer cuff was inflated on the upper arm to a pressure of 80–100 mmHg above systolic blood pressure. Hand temperature was monitored on skin adjacent to the thermode, using a digital thermometer (2100 Tele Thermometer, VSI, Yellow Springs, Ohio). It was maintained within 1° C of baseline temperature by a radiating heat source. Compression-ischaemia was sustained for 1 h or until the volunteer requested release due to discomfort or pain underneath

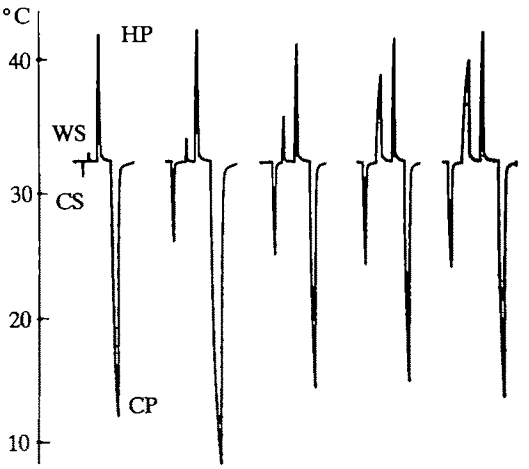

FIG. 1. Actual QTT record of subject B.T., abbreviated to present only one response per stimulus series in only 5 series. In each series, the first deflection (left) is for cold sensation (CS), followed by warm sensation (WS), heat pain (HP) and cold pain (CP). After an initial threshold increase (distraction), cold pain thresholds decrease to peak at 30 min. Thereafter, thresholds increase again, that is, lower temperatures are required to reach threshold.

the cuff. Thermotest threshold measurement was performed repeatedly throughout the test session and was supplemented by routine sensory testing, including light mechanical (brush), intense mechanical (pin prick) and low temperature (brief application, for less than 10 s, of an ice cube) stimuli, applied to the hairy skin on the dorsum of the hand. In addition to signalling thresholds, the subject was asked to describe verbally the subjective quality of the sensation evoked by such stimulation. In order to avoid anticipatory responses, the sequence of presentation of the thermal stimuli was changed randomly from one cycle to the next. However, the two thermal specific sensations always preceded the thermal pains. Results for high temperature stimulation will be reported separately.

RESULTS

The study was performed on 19 volunteers, 7 males and 12 females, aged 19–50 (mean 34) yrs. The right hand was used in 12 subjects and the left in 7. Four volunteers kept the cuff on for a full hour while the other 15 failed to endure this duration because of local pain at the site of the cuff. Mean cuff time was 43.37 ± 2.36 (SEM) min (range 27–60 min). Mean time for loss of sensation evoked by light brushing of the skin was 21.68 ± 0.99 min. Subjects started reporting a change in the sensation induced by pin prick at 20.94 ± 2.53 min. This consisted of a transformation from sharp to dull pain in 14 subjects, to 'something' in 2 and to no sensation in 1. No change in the sensation induced by pin prick was reported by 2 subjects.

Cold sensation

In 14 subjects the quality of the *first sensation* evoked by a low temperature stimulus applied by the QTT probe changed at 21.14 ± 2.39 min (mean ± SEM). After this time, 11 described it as either hot (8) or burning (3), 1 as 'something' with no temperature quality, 1 as pain and 1 as a sting. Five other subjects kept reporting cold throughout the compression-ischaemia block period, which lasted 27, 33, 38, 42 and 60 min, respectively. However, in the first 2 of these 5 subjects, while the sensation of cold induced by the thermode was unchanged, a sensation of cold was not induced by brief application of ice cube (at 23 and 17 min, respectively). This differential response suggests that these 2 subjects were on the verge of cold sensation block at the relatively early time of removal of the cuff.

When examining individual charts disclosing the evolution of threshold for the sensation of cold during the course of a block, the usual pattern was an early increase in threshold, in the first 5 min, which is thought to result from the distraction induced by the inflation of the cuff (Kojo and Pertovaara, 1986). Thereafter, thresholds for cold sensation became fairly stabilized for up to 15 min, beyond which they became elevated to reach eventually a final plateau at much lower temperature than baseline (fig. 1). As the timing for this change is different in different individuals, the details of this pattern are blurred in the averaged illustration (fig. 2), which shows a gradual threshold increase (reduction in required stimulus energy), reaching a plateau at about 25 min. The mean threshold at baseline was 30.46±0.34° C. After 5 min mean threshold was 28.06±0.33 and at 30 min of cuff 24.83±0.91° C. Comparing either baseline thresholds or the results of 5 min with those at 30 min of block yielded a significant difference ($P < 0.001$, Wilcoxon test).

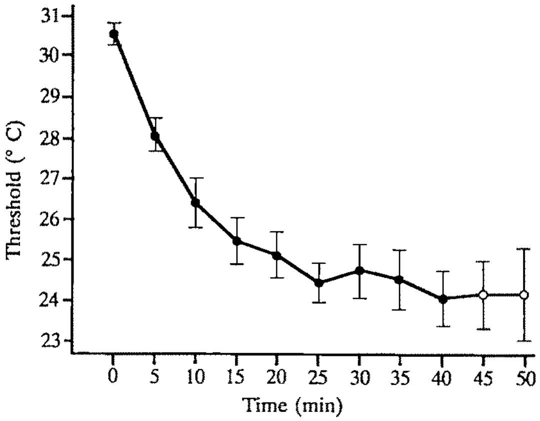

FIG. 2. Mean cold sensation thresholds along the course of block (° C ± SEM). Thresholds obtained at 45 min and later are drawn as open circles; they represent the few subjects that tolerated the cuff for that duration.

Low temperature-induced pain

The pain induced by a low-temperature stimulus ramp applied through the QTT probe changed in quality from 'cold' and usually 'aching', to 'hot' or 'burning' sensation in 13 of the 19 subjects at 20.36±2.33 min. In 3 subjects the subjective response became pain without a thermal quality and in yet another 3 it remained unchanged throughout the test. Similar results were obtained by applying the ice cube: in 11 subjects the sensation became hot or burning (at 22.38±1.31 min), in 4 it became pain with no thermal quality, in 1 the ice induced a sensation of touch (at 24 min) and in 3 the sensation was unchanged throughout the block.

The mean baseline threshold for cold pain was 13.43 ± 1.24° C. Following a slight increase in threshold immediately after cuff inflation, cold pain thresholds disclosed a biphasic profile of change (fig. 3). Stage I, as observed in 17 subjects, consisted of gradual decrease in thresholds (pain was signalled at less low temperatures), reaching a peak at 27.3 min on average (range 15–55 min). The mean threshold at peak was 20.02 ± 1.16° C, significantly different from the baseline value ($P < 0.001$, Wilcoxon signed rank test). Stage II was expressed in 15 subjects, and consisted of a weak reversal of thresholds towards baseline. The temporal relationship between the changes in thresholds for cold sensation and for cold pain is shown in fig. 4.

No	*Subject*	*Age (yrs)*	*Sex*	*Duration*
1	D M	36	F	46
2	B T	34	M	41
3	M R	35	M	31
4	L.B	36	F	40
5	D Y	30	M	60
6	R.K.	34	M	60
7	J S.	50	F	50
8	C.S	19	F	44
9	K.P.	47	M	47
10	E B	23	F	60
11	C B.	33	F	38
12	S.F.	27	F	45
13	E J.	28	M	27
14	G H	29	M	33
15	L.D.	38	F	32
16	C D	18	F	35
17	J B.	41	F	42
18	M.B.	18	F	42
19	S.C	34	F	43

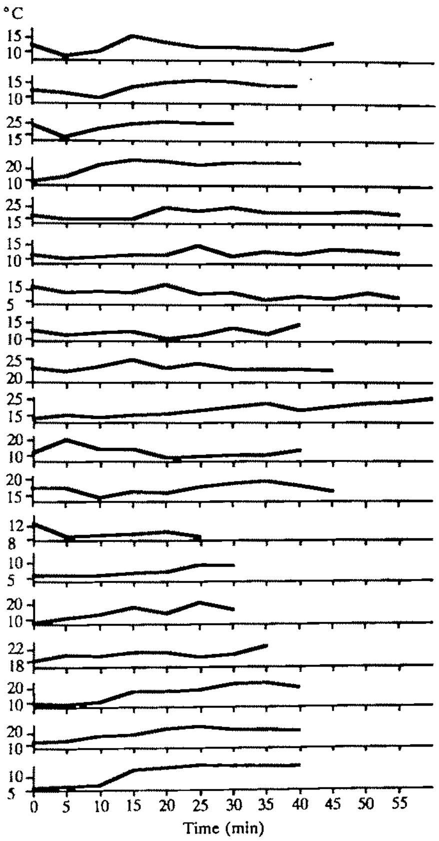

FIG. 3. Individual profiles of cold pain thresholds for all subjects during the course of the block. Apart from subjects 11 and 13 (who tolerated the block for the shortest time), with time all subjects exhibited decrease in cold pain thresholds (less cooling required to reach threshold).

Two subjects failed to reveal any well defined trend in the evolution of their cold pain thresholds during the block.

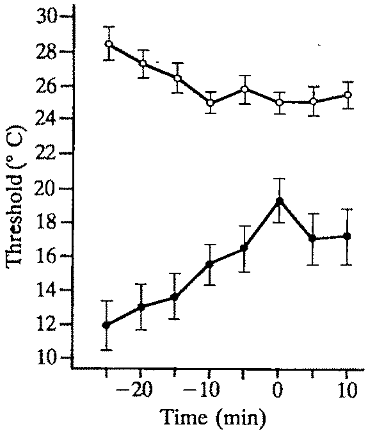

FIG. 4. Mean thresholds for cold sensation (open circles) and cold pain (filled circles). After centring individual records, around the time of lowest threshold for cold pain (time 0), all thresholds along the time sequences were averaged. The increase in thresholds for cold sensation is clearly paralleled by the decrease in those for cold pain.

DISCUSSION

The primary afferent channels conveying the neural message elicited by mild low-temperature stimuli are widely accepted as being subserved by small calibre myelinated fibres (A delta). This concept is based on direct stimulus response data obtained through recordings of physiologically identified single afferents in animals (Darian-Smith *et al.*, 1973; Georgopoulos, 1976) and man (Adriaensen *et al.*, 1983). Supporting evidence is provided by human psychophysical studies on cold sensation, either through differential nerve fibre blocks (MacKenzie *et al.*, 1975; Fruhstorfer, 1976) or through reaction time measurement (Fruhstorfer, 1976; Fowler *et al.*, 1988).

There is also evidence for participation of primary unmyelinated afferents in the conduction of impulses induced by low-temperature stimuli. Firing in animal C nociceptors in response to low-temperature stimuli, of both mild and noxious intensity, has been recorded by several investigators (Georgopoulos, 1976; Kumazawa and Perl, 1977; LaMotte and Thalhammer, 1982; Saumet *et al.*, 1985), after other investigators had reported minimal or no response (Bessou and Perl, 1969; Croze *et al.*, 1976). In man, only a handful of C nociceptors responding to cooling have been recorded (Torebjörk and Hallin, 1973; Yarnitsky and Ochoa, unreported observations).

Participation of A delta *nociceptors* in the transmission of impulses triggered by noxious cold stimuli has been described for the trigeminal system in animals (Jyväsjärvi and Kniffki, 1987; *see* review by Sessle, 1987) and is consistent with human psychophysical correlates of first and second cold pain (Kniffki *et al.*, 1988). We believe that in the present study the cold pain message had no A delta nociceptor contribution since none of our subjects reported a double pain before or during the test, as did Kniffki's subjects when exposed to noxious cold stimuli to their teeth.

We conclude, therefore, that when delivering a noxious low-temperature stimulus to our subjects, afferent activity was induced in two specific types of afferent channels, as suggested by LaMotte and Thalhammer (1982) and by Saumet *et al.* (1985). One type of channel conducts the cold message and is subserved by small myelinated A delta fibres, and the other conducts the pain message subserved by unmyelinated C nociceptors. Their cooperative actions result in the blended sensation of cold and usually aching pain.

Sensory processing during compression-ischaemia block might, in theory, be altered by cuff-induced pain and by metabolic ischaemic changes. However, the remarkable consistency of thresholds for heat-induced pain throughout the block session in all volunteers (Yarnitsky and Ochoa, unreported observations) indicates that in the present experiment pain perception was independent of these factors. Further, it was the subjective impression of all subjects that pain at the cuff site was clearly distinguishable from sensations evoked distal to it.

During A fibre block, a novel quality of pain, hot or burning, was induced by low-temperature stimuli applied either by the QTT probe or by an ice cube, a quality known to be induced by pure activation of human C nociceptors through intraneural microstimulation (Ochoa and Torebjörk, 1989). Since none of the subjects experienced this burning pain quality before block, when all pertinent afferent channels were available to conduct the message, it can be concluded that the afferent input normally elicited by noxious low temperature undergoes modulatory interaction. The burning subjective quality of the pain evoked by C nociceptors would normally be suppressed by another coexisting afferent barrage.

This interaction, moreover, not only affects the subjective quality attribute of the sensation, but it also affects its magnitude. Since with progressive block a sensory function should not be expected to improve, that is to reduce threshold, then the only reasonable explanation for the decreasing thresholds of pain induced by low temperature, as observed in stage I, is disinhibition. It may be hypothesized that under normal conditions, the neural message induced in myelinated fibres by a low-temperature stimulus inhibits the message evoked in unmyelinated fibres by the same stimulus. Although the most likely channel to exert this gating is the cold-specific channel, the present results cannot exclude involvement of other myelinated channels activated by this stimulus. Previous evidence by Bini *et al.* (1984) showing an increase in intraneurally-induced pain thresholds by cooling the cutaneous projective field also suggests that the cold-specific channel exerts pain inhibition.

As block progresses and myelinated afferent channels are less and less available, the inhibition becomes weaker, allowing the cold pain threshold to decrease, although enough cold-specific afferents are still available to mediate a residue of cold aching pain. Next, the cold-specific channels are closed, and the message induced by noxious low temperature is carried exclusively by nociceptors. This releases a burning pain, at a relative low threshold, demonstrated as the peak threshold in fig. 3. Later, as C nociceptors themselves start blocking, in order to compensate for loss of spatial summation, increased temporal summation is needed to reach threshold for pain. This explains the increasing thresholds for cold pain in stage II.

The general idea of central 'gating' of sensory information has been entertained by sensory physiologists for decades (Head, 1921; Noordenbos, 1959; Wall, 1978). More specifically, gating of the input of C nociceptors that convey the pain fraction of the cold pain message, exerted by cold-specific A delta afferent input carrying its cold fraction, was proposed by LaMotte and Thalhammer (1982) as an explanation for the observation that monkey C nociceptors fire in response to presumably innocuous low temperature stimuli (20° C). Further evidence was contributed by Bini *et al.* (1984), as described previously. Those results support our assumption, discussed above, that of the sensory submodalities served by myelinated fibres, it is the cold-specific input that exerts the gating. This mechanism provides an alternative to Fruhstorfer's proposal of the existence of a special class of low threshold, *cold-specific* unmyelinated receptors sensing a 'dysaesthetic' cold sensation when myelinated fibres are blocked (Fruhstorfer, 1984). Instead, it is proposed here that the high threshold C nociceptors evoke a pure unblended pain quality, at a reduced threshold, due to removal of modulation normally exerted by the A delta myelinated mediated fraction of the cold pain message. A recent study (Wahren *et al.*, 1989) used direct nerve compression as a means of blocking A fibres selectively, and reached similar conclusions regarding the qualitative and quantitative changes in the perception of pain induced by low-temperature stimuli. Admittedly, the present results have been interpreted strictly in accordance with the specificity theory of somatic sensation, and in these terms the explanation seems highly plausible. The authors find it difficult to reconcile the results in terms of pattern theory.

Disinhibition is not the only mechanism for low temperature to suppress pain. Cooling can disable the sensory apparatus by either blocking nerve impulse conduction (Franz and Iggo, 1968) or by desensitizing normal receptors (Kunesch *et al.*, 1987). Such effects are probably not pertinent to the present study, since in the experiments of Franz and Iggo temperatures below 10° C were applied directly to the nerves, and in the study by Kunesch *et al.*, prolonged cooling for at least 3 min was applied. Such extreme conditions were not used in our study; QTT probe temperature seldom dropped below 10° C, and stimulation time was less than 30 s, while application time of ice cube was less than 10 s.

An abnormally released interaction between the two channels—cold-specific and nociceptor-specific—is perhaps expressed in certain neuropathic pain patients who complain that their symptomatic limbs 'burn' when cold. Quantitative sensory testing of thermal specific and thermal pain thresholds from limbs of such patients shows the low-temperature stimulus to be perceived as warm-burning, associated with elevated cold sensation thresholds, suggesting functional deficit of cold related A delta fibres. A noxious low-temperature stimulus may thus induce an ungated pain message, evoking a sensation of burning pain (Ochoa and Yarnitsky, 1990). The observation by Kashihara and Yabuki (1987) that in 2 patients with Guillain-Barré syndrome, low-temperature stimuli were felt as burning, can also be explained by the proposed mechanism, since the disease process is expected to disrupt function in the cold-specific A delta myelinated fibres, but not the nociceptor unmyelinated fibres.

In conclusion, psychophysical evidence is hereby raised to support the hypothesis that when a noxious low-temperature stimulus is given, the cold-specific message gates the pain message, 'protecting' the subject from excessive pain. In other words, cooling may be an active way to relieve pain.

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TYPE I FAMILIAL AMYLOID POLYNEUROPATHY

A PATHOLOGICAL STUDY OF THE PERIPHERAL NERVOUS SYSTEM

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SUMMARY

The neuropathological changes were examined in 2 cases of type I familial amyloid polyneuropathy (FAP), confirmed by a genetic study with human transthyretin (prealbumin) cDNA. These cases were from different foci of type I FAP in Japan, but showed a similar pathology in the peripheral nerves. Loss of dorsal root and sympathetic ganglion neurons, predominantly those of small size, was prominent, whereas ventral horn cells were well preserved. Distally accentuated axonal loss with marked axonal sprouting was the principal feature. Fibre sprouts were ubiquitous throughout the nerves and affected the fibre size distribution. Segmental demyelination and remyelination were prominent in the proximal portions of nerves, but axonal degeneration was more conspicuous in the distal portions. The centrally-directed branches of the primary sensory neurons did not show distally-accentuated axonal loss in the dorsal columns. Amyloid deposits were present universally in the endoneurial spaces of the peripheral nerves, but more prominently in the dorsal root ganglia, sympathetic ganglia and more proximal portions of the nerves, and the distribution correlated well with the occurrence of the pathology of peripheral nerves. Neurofilamentous accumulation was frequent in the proximal axons and neuronal cell bodies of the sensory and sympathetic neurons. Schwann cells and satellite cells to which amyloid deposits were attached frequently showed disappearance of basement membrane and proliferation of distorted processes.

The findings in the present cases suggest that the Schwann and satellite cells may be directly affected by the amyloid deposits, but the pathogenetic mechanism of marked axonal and neuronal involvement still remains to be elucidated.

INTRODUCTION

Familial amyloid polyneuropathy (FAP) was first described by Andrade (1952) in Portugal. Since that report, many patients with similar disorders have been reported in several countries. Currently, FAP is classified into at least 7 subtypes (I–VII; Holt *et al.*, 1989), based on the clinical manifestations and the site of the point mutation in the human prealbumin (transthyretin, TTR) gene. Type I FAP is the most common and is characterized by the initial development of a sensory and autonomic neuropathy,

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predominantly in the lower legs, followed by motor neuropathy. So far it has been described in Portuguese (Andrade, 1952; Coutinho *et al.*, 1980), Japanese (Araki *et al.*, 1968; Kito *et al.*, 1980), Swedish (Andersson, 1970, 1976; Benson and Cohen, 1977), Irish (Staunton *et al.*, 1987), English (Zalin *et al.*, 1974; Mahood, 1980), Greeks (Dyck and Lambert, 1969; Thomas and King, 1974; Holt *et al.*, 1989), Germans (Cohen and Rubinow, 1984), and in Portuguese immigrants in several countries. The abnormality at the molecular level in type I FAP is an amino acid substitution in TTR at position 30 (methionine-for-valine, 30 val → met) (Costa *et al.*, 1978; Skinner and Cohen, 1981; Tawara *et al.*, 1983; Dwulet and Benson, 1984; Saraiva *et al.*, 1984; Nakazato *et al.*, 1984, 1987; Sasaki *et al.*, 1984, 1985), although this substitution was not demonstrated in all the above descriptions of type I FAP. In Japan, a large focus of patients with type I FAP was first reported by Araki *et al.* (1968) from Arao City on Kyushu Island, and subsequently described in Ogawa village in Nagano Prefecture in the middle of Honshu Island (Kito *et al.*, 1980). Recently, patients with atypical clinical features involving the central nervous system and still having 30 val → met substitution of TTR have been reported in the latter area (Furuya *et al.*, 1987; Ikeda *et al.*, 1987), but most clinical features of the patients from these two large foci in Japan are identical to those reported in Portugal. In spite of recent progress in biochemical and genetic characterization of abnormal TTR found in this disease and in its diagnostic application (Nakazato *et al.*, 1984, 1987; Sasaki *et al.*, 1984, 1985; Benson and Dwulet, 1985; Mita *et al.*, 1986), the pathogenetic mechanism of peripheral neuropathy is not well understood. Reports on autopsied cases are not uncommon (Andrade, 1952; Shirabe *et al.*, 1973; Hofer and Andersson, 1975; Guimarães *et al.*, 1980; Delisle *et al.*, 1983; Sumino *et al.*, 1983; Yamada *et al.*, 1984; Hanyu *et al.*, 1989) but the clinicopathological analysis, particularly as to how amyloid deposits give rise to the damage in the peripheral nerves, and how the pathology correlates with the clinical features such as the predilection for the autonomic nervous system, sensory dissociation, and a monophasic pattern of clinical progression, has been discussed mainly on the basis of findings on sural nerve biopsy (Dyck and Lambert, 1969; Coimbra and Andrade, 1971*a*, *b*; Ohta *et al.*, 1974; Takahashi *et al.*, 1974; Thomas and King, 1974; Carvalho *et al.*, 1976; Araki *et al.*, 1978; Said *et al.*, 1984).

In this report, we describe the results of the systematic examination of the peripheral nervous system in 2 autopsied cases of type I FAP from two areas within the large focus in Japan, with proof of 30 val → met substitution at the TTR gene level.

PATIENTS AND METHODS

Case 1

Female, aged 51 yrs; most of her maternal and paternal relatives were residents of Arao City on Kyushu Island. She had 4 affected siblings and also affected relatives in 3 preceding generations indicating autosomal dominant inheritance (fig. 1A). She began to experience attacks of syncope at the age of 37 yrs, and was diagnosed as having the sick sinus syndrome, and received an implanted cardiac pacemaker. Over the next 2 yrs she noted intermittent shooting pains in the distal portions of the lower legs. Since then she has sustained occasional painless burns on the feet. At about the age of 40 yrs, she noticed difficulty in walking and became unable to run. Shooting pains also appeared in the arms. Constipation, followed by severe diarrhoea, and occasional urinary incontinence also occurred. Neurological examination, at the age of 45 yrs, showed that she was intelligent and well-orientated but she was unable to stand and could barely walk, which she accomplished by pushing a wheelchair. Her pupils were irregular in shape and did not react to light. Muscle strength was moderate to severely diminished in the legs, and moderately in the forearm and hand muscles. Muscle atrophy was present mainly in the lower legs. The tendon reflexes were preserved in the upper limbs, but virtually absent in the legs. The plantar responses were not extensor. Pin prick and light touch sensation was moderately impaired over the trunk and upper limbs, and severely in the legs and hands. A localized area of sensory loss was also observed over the anterior abdominal wall. Vibration and joint position sense was almost completely lost in the distal portion of the legs, but more mildly impaired elsewhere, as compared with touch and pain sensation. Sweating was severely diminished in the legs. There was orthostatic hypotension, reduced salivation and lachrymation. Sensorineural deafness, predominantly on the left, was present. Nerve conduction studies revealed a severe diminution of motor conduction velocity (median, 20.5 $m \cdot s^{-1}$; ulnar, 36.6 $m \cdot s^{-1}$; tibial, 16.0 $m \cdot s^{-1}$) and absence of sensory action potentials (distal median and sural nerves). The cerebrospinal fluid was normal. Creatinine clearance was moderately reduced (38 $ml \cdot min^{-1}$), but urinalysis, blood chemistry, haematology and routine serological examination were normal.

She had been confined to a wheelchair from the age of 47 yrs. Alternating constipation and diarrhoea then became uncontrollable, and persistent ulceration of the sacrum and feet developed. Urinary infections were frequent. An upper respiratory infection followed by cardiac failure led to her death. Autopsy was performed 3 h postmortem.

Case 2

A 41-yr-old man first noticed alternating constipation and diarrhoea at the age of 24 yrs. He subsequently became impotent. When he was aged 32 yrs, occasional syncopal attacks occurred and he was found to have a second degree A-V conduction block. Shooting pains in the legs also occurred. There was diminished thermal and pain sensation in the legs, and painless burns in the legs produced by a brazier or stove were frequent. Subsequently, difficulty in walking and in skilful hand and finger movements became evident. The clinical manifestations observed in the fully developed state of this patient were almost identical to those in Case 1. Most of his family were residents of Ogawa village in Nagano Prefecture and autosomal dominant inheritance of the disease was indicated (fig. 1B). Infection from a large ulcer in the sacral region and subsequent cardiac failure were the cause of death. Autopsy was performed 4 h postmortem.

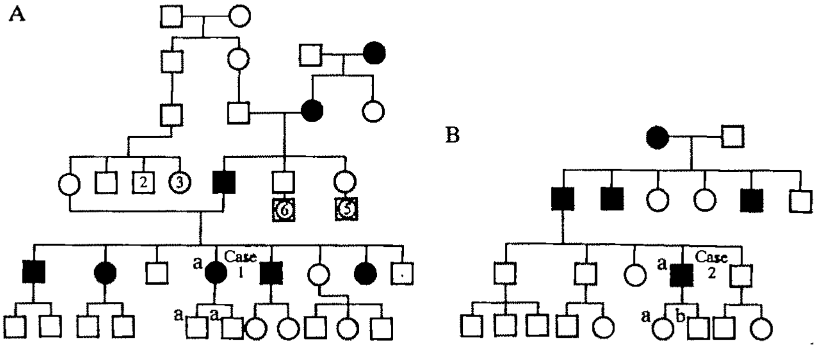


FIG. 1. Family pedigrees of *Cases 1* (A) and 2 (B). [a]Diagnosed as having a mutation of the TTR gene by recombinant DNA techniques; [b]diagnosed as not having a mutation by recombinant DNA techniques.

DNA analysis

The mutation in the TTR gene from both cases was analysed; the results have been published elsewhere (Sasaki *et al.*, 1984, 1985). Briefly, DNA prepared from leucocytes was digested with the restriction endonucleases Nsi I or Bal I and subjected to Southern hybridization analysis with TTR cDNA as a probe (Sasaki *et al.*, 1985). DNA from both cases gave the bands typical for FAP (5.0 and 1.4 kb with Nsi I, 3.6 and 1.6 kb with Bal I) (Sasaki *et al.*, 1984). The children of Cases 1 and 2 were also examined in the same manner; this revealed that 2 sons of Case 1 and 1 daughter of Case 2 gave the same hybridization pattern, indicating the same mutation in TTR gene in their DNA (Sasaki *et al.*, 1985; fig. 1).

Neuropathological methods

The brain, the whole spinal cord, dorsal root ganglia from L3 to L5, thoracic sympathetic ganglia and muscles from the upper and lower limbs were removed and fixed in 10% buffered formalin and embedded in paraffin wax. Sections were generally stained with haematoxylin and eosin, and by the Klüver-Barrera, Holzer and Bodian methods in some instances. Sections from most of the specimens were also stained with Congo red and examined with polarization optics.

Whole median nerves from the axilla to the wrist, and sciatic and tibial nerves from the upper thigh to above the medial malleolus, were removed and suspended in a glass cylinder with a weight and fixed in 1.5% glutaraldehyde, 3% formalin 0.05 M phosphate buffer, pH 7.4 for 16 h. Plastic-embedded 1 μm sections were obtained from samples taken every 3 cm along the nerves after postfixation in 2% osmium tetroxide in the same buffer. The ventral and dorsal spinal roots, segmental nerves and femoral nerves were also removed and fixed and processed in the same manner. The density of myelinated fibres in toluidine blue-stained semithin sections was calculated from photographs at a magnification of ×1000 by using a particle size analyser (Zeiss TGZ-3) as described previously (Dyck *et al.*, 1978; Sobue *et al.*, 1981, 1986*a*, *b*). Since myelinated fibres were distributed unevenly between the fascicles, photographs were taken randomly of locations that showed at least 3 fascicles in the same transverse section of the nerves.

For electron microscopy, parts of the dorsal root ganglia, sympathetic ganglia, sciatic and median nerves were fixed in 2% glutaraldehyde in 0.1 M phosphate buffer, postfixed in 2% osmium tetroxide in the same buffer, and processed for ultrathin sections. Some specimens fixed with 10% buffered formalin, and embedded in paraffin wax, were deparaffinized with xylene and processed for immunohistochemistry for human TTR and phosphorylated neurofilaments (Ta 51), as described before (Sobue *et al.*, 1988), using antihuman TTR rabbit polyclonal IgG (Dako Laboratories) and monoclonal antibody against phosphorylated high molecular weight neurofilaments which was a generous gift from Dr Trojeanowski, University of Pennsylvania.

Isolated single nerve fibres were prepared from specimens obtained at various levels, and the pathological condition of each fibre was classified according to previously described criteria (Sobue *et al.*, 1981, 1989).

A 59-yr-old woman who died from a cerebral haemorrhage served as a control.

PATHOLOGICAL FINDINGS

Spinal, sciatic, tibial and median nerves

The myelinated fibre population in the spinal nerves was severely diminished (fig. 2A). Large clusters of small diameter, thinly myelinated fibres, corresponding to regenerating sprouts, were frequent (fig. 3A). In the sciatic and tibial nerves in both patients, myelinated fibres were almost completely absent (fig. 2A). Diameter-frequency histograms of myelinated fibres along these nerves showed that small-sized myelinated fibres, probably representing regenerating fibres, were relatively frequent in the spinal nerves (fig. 2A).

Myelinated fibres in the median nerves (fig. 2B) were relatively well preserved, particularly as compared with those in the sciatic and tibial nerves (fig. 2A). There was also a significant proximal to distal gradient of axonal loss, but small myelinated fibres were considerably more numerous, particularly in more proximal portions (fig. 2B, 3B); levels 1–5 or 6 (fig. 2). Clusters of small myelinated fibres, representing nerve sprouts, were also prominent in the more proximal portions of the median nerves (figs 3B, 4). Except for these clustered fibres, small myelinated fibres in the endoneurium were fewer than those of large diameter (fig. 3B), suggesting that most of the small fibres were sprouts, and small fibres may be preferentially involved in the primary process. Unmyelinated axons were severely depleted throughout all nerves, even in the proximal portions where myelinated fibres were still numerous. In teased fibre preparations, there was a considerable increase in fibres with segmental demyelination and remyelination, often clustered along a single fibre, particularly in the proximal portions (fig. 5; Table 1). Axonal degeneration was more prominent in the more distal portions of the nerve (Table 1). Accumulations of neurofilamentous material, mitochondria and small dense lamellar bodies in swollen axons were occasionally observed in both myelinated and unmyelinated axons (fig. 6).

Amyloid deposits demonstrated by Congo red staining, immunohistochemistry against human TTR and electron microscopy were ubiquitous throughout the endoneurium of the nerves. They were either related to the endoneurial vessels or seen as solitary deposits. Although quantification of amyloid deposits was not performed, they were probably more frequent in the proximal and middle portions than in the more distal portions of these nerves (Table 2). They were often directly associated with the basement membrane of Schwann cells, which was often absent. Distorted Schwann cell processes frequently containing increased numbers of intermediate fibrils were conspicuously present at the margins of the amyloid deposits. Appearances showing that amyloid deposits compressed the myelinated fibres were also ubiquitous, and were most clearly demonstrated in the teased fibre preparations (fig. 5).

The basement membrane of endoneurial capillaries associated with amyloid fibrils was often reduplicated and redundant, but the lumen of these capillaries was usually patent.

Dorsal root ganglia, dorsal roots and posterior columns

The dorsal root ganglia were enlarged in overall size, and amyloid deposits were noted in the interstitial, subcapsular and perivascular spaces. Neurons in the dorsal root ganglia were severely depopulated. Small-diameter neurons seemed preferentially lost (fig. 7). Accumulated neurofilamentous material and distorted cell organelles in the margin of the enlarged axoplasm were frequently seen (fig. 8B). Numerous spheroids filled with phosphorylated neurofilaments were also seen by light microscopy (fig. 8A). A mass with degenerated cell organelles, probably originating from degenerated axons or neurons, was seen within an amyloid deposit. Redundant and distorted cytoplasmic processes and increased intermediate filaments were present in satellite cells that were surrounded by amyloid fibrils.

In the dorsal spinal roots, lobulated deposits of amyloid fibrils were conspicuous and distorted the myelinated fibres (figs 3C, 9). Both large and small myelinated fibres were severely depleted, but depopulation of small-sized myelinated fibres was more prominent (fig. 3C, 9). Clusters of small myelinated fibres were, however, infrequent, particularly as compared with the ventral roots, spinal, and median nerves.

Myelin pallor was present in the fasciculus gracilis without amyloid deposition. This myelin pallor was seen at all segmental levels of the posterior columns, and there was no apparent rostrocaudal gradient in its intensity. Morphometric analysis indicated no significant rostral accentuation of axonal loss in the dorsal columns (fig. 9).

Ventral horn cells and ventral spinal roots

The population of the ventral horn cells was well preserved, but a central chromatolytic response was frequently observed. In the ventral spinal roots, amyloid deposits were rare, particularly as compared with the dorsal spinal roots, and myelinated fibres were quite numerous. Clusters of small myelinated fibres, and occasionally of large ones, were frequent and the former may correspond to the increased population of small myelinated fibres seen in the fibre-size histogram (fig. 10).

Neurons in the intermediolateral columns, thoracic ventral roots and sympathetic ganglia

Neuronal populations in the intermediolateral columns were apparently well preserved, although quantitative studies were not undertaken. Small thinly myelinated fibres in the ventral roots were, however, considerably depleted.

The sympathetic ganglia were enlarged in overall size and amyloid deposits were prominent in the interstitial, subcapsular and perivascular spaces. The neuronal population was dramatically decreased, and neuron-size analysis disclosed that the decrease occurred more prominently in those of small size (fig. 7). The remaining neurons mostly showed an apparently normal structure, but an accumulation of

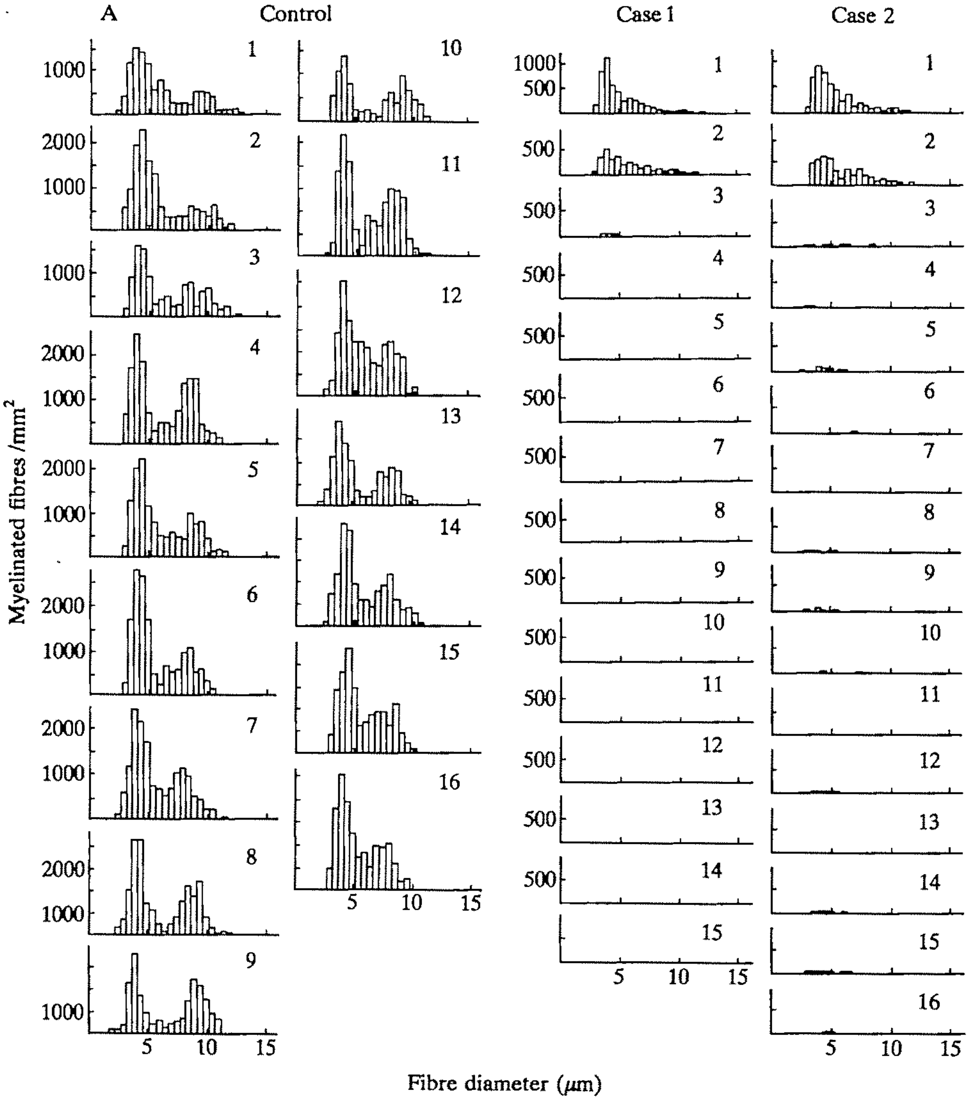


FIG. 2A.

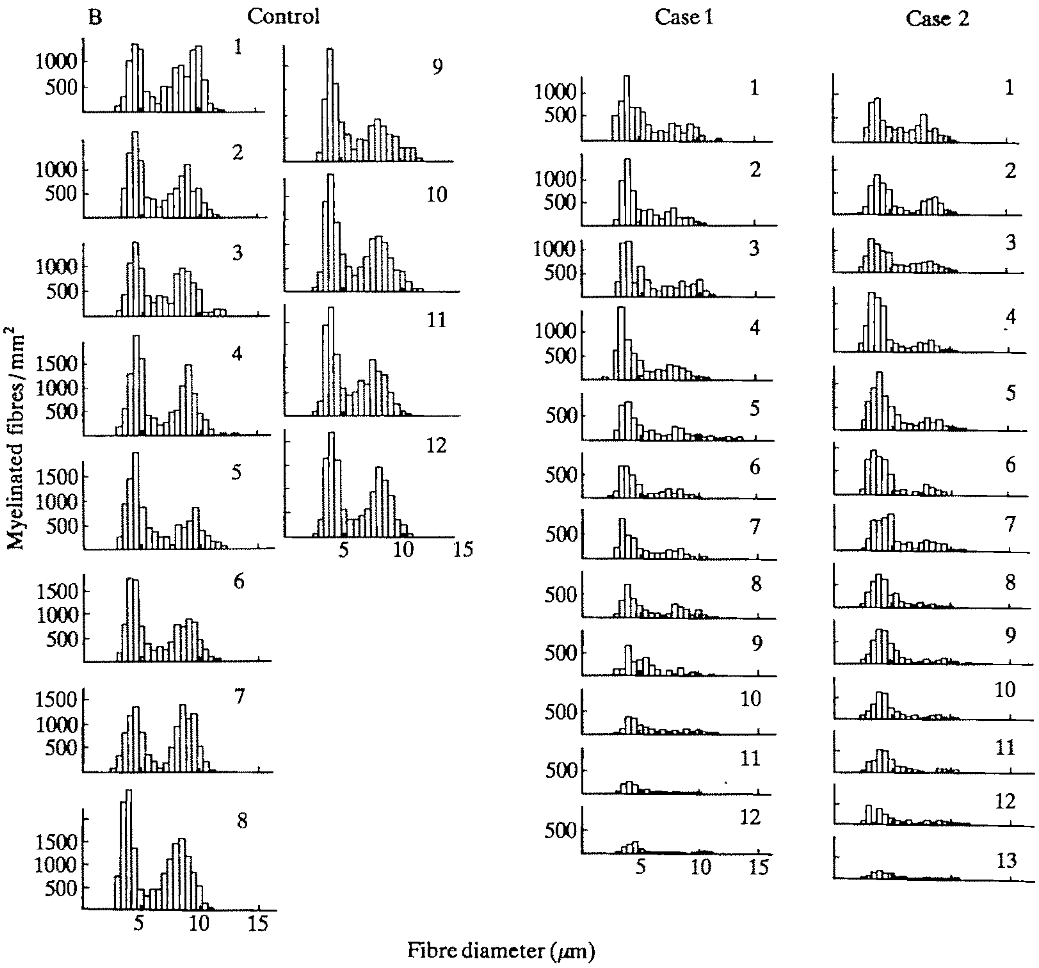
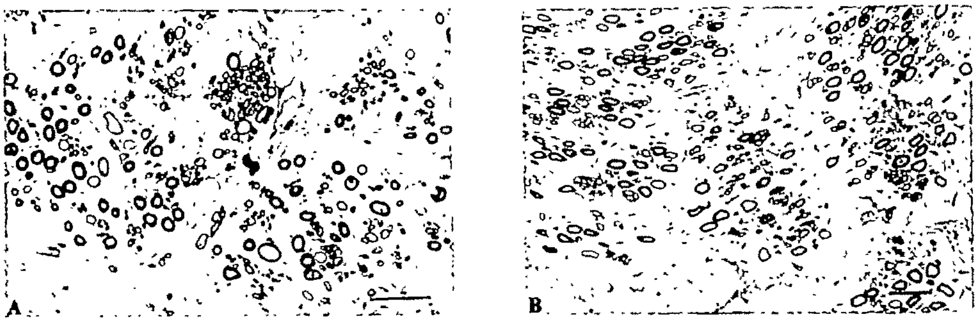


FIG. 2. Diameter-frequency histograms of myelinated fibres in consecutive portions along the spinal, sciatic and tibial (A), and median (B) nerves. The numbers in each panel indicate the consecutive proximodistal locations in each nerve.

neurofilamentous material was seen in spheroids (fig. 8c) and in some neuronal perikarya. Multilamellated distorted processes of satellite cells, particularly associated with amyloid deposits similar to those in the dorsal root ganglia, were also frequently seen.

Other structures of the spinal cord and CNS

Neurons in Clarke's column were numerous. Myelinated fibres in the long tracts of the spinal cord other than the posterior columns were well preserved. Neurons in the gracile and cuneate nuclei were also numerous. Amyloid deposits were observed in the subarachnoid and subpial spaces and in the choroid plexuses but not in the parenchyma of the CNS, and the morphology of the CNS appeared to be normal. Prominent Schwann cell proliferation resulting in Schwannoma-like masses was often seen in the anterior median fissure or in the grey matter of the spinal cord in both patients.



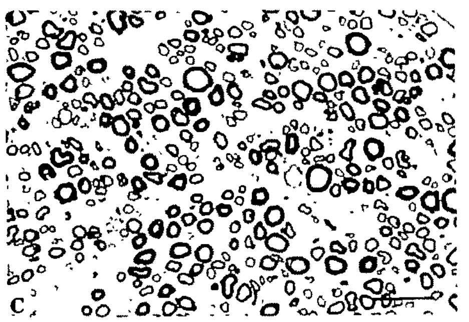


FIG. 3. A, transverse section of L4 spinal nerve (*Case 2*). Large clusters of fibre sprouts are seen. Toluidine blue. B, transverse section of the proximal portion of the median nerve (*Case 1*). Clusters of fibre sprouts are conspicuous. Toluidine blue. C, transverse section of L4 dorsal root (*Case 2*) showing prominent loss of small myelinated fibres. Toluidine blue. Bars = 22 μm.

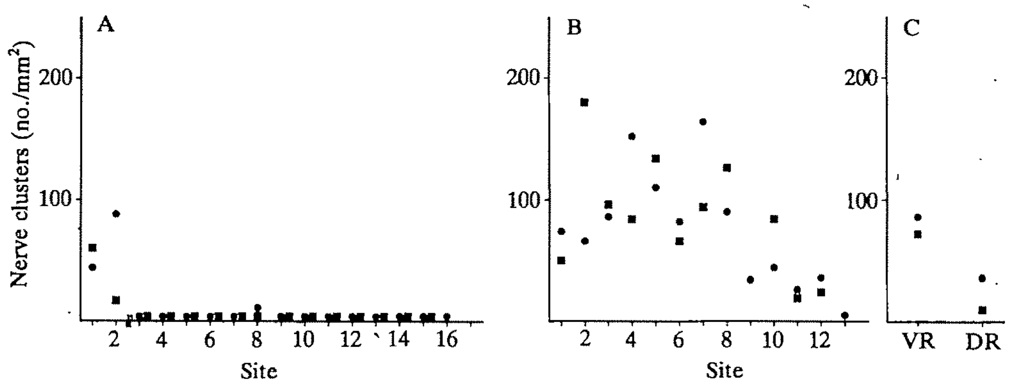


FIG. 4. Incidence of clusters of small myelinated fibres in the spinal, sciatic and tibial nerves (A), median nerves (B), and L4 spinal ventral and dorsal roots (C). 'Clusters' were defined as assemblies of more than 3 small myelinated fibres. ×1000. Squares = *Case 1*, circles = *Case 2*.

DISCUSSION

The 2 cases described in this study were diagnosed on clinicopathological grounds as type I FAP (Andrade, 1952; Hersch and McLeod, 1987) and this was confirmed by a genetic study with human TTR cDNA (Sasaki *et al.*, 1984, 1985).

Selectivity in size-dependent axonal loss has been the subject of discussion in relation to the clinical manifestations (Dyck and Lambert, 1969; Thomas and King, 1974; Said

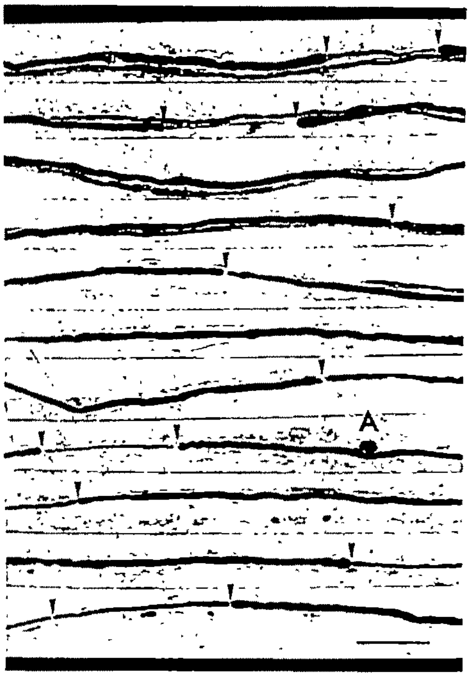


FIG. 5. Consecutive portions along the length of a single teased fibre from the proximal portion of the median nerve from *Case 1*. Multiple remyelinated internodes are seen. Osmium tetroxide. A = amyloid deposit. Bar = 30 μm.

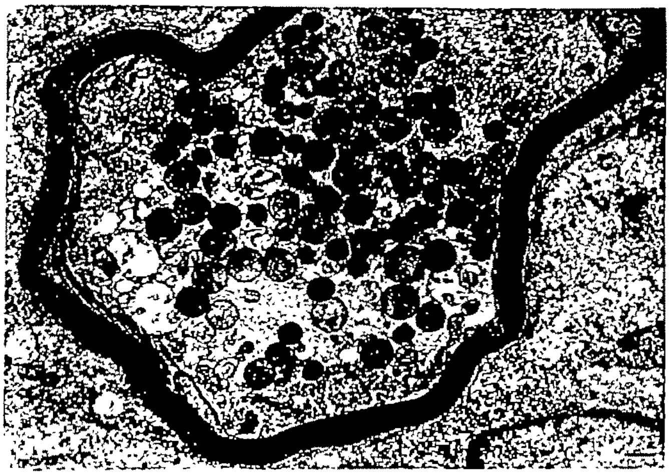


FIG. 6. Electron microphotograph of median nerve (*Case 1*) showing accumulation of mitochondria and other cell organelles in an enlarged axon. Bar = 0.5 μm.

et al., 1984). Some reports have stated that a preferential depopulation of unmyelinated and small myelinated axons occurs (Dyck and Lambert, 1969; Thomas and King, 1974), and that this finding correlates with the preferential involvement of pain and temperature sensation and of autonomic function. Some other reports, however, have insisted that the large myelinated fibres are predominantly decreased (Araki *et al.*, 1978), or that fibre loss is independent of size (Takahashi *et al.*, 1974; Yamada *et al.*, 1984).

TABLE 1. TEASED-FIBRE STUDY*

	Normal appearance	*Axonal degeneration*	*Segmental demyelination and remyelination*
Proximal median nerve (level 1)			
Case 1	62.3	14.8	22.9
Case 2	53.2	12.8	34.0
Control	93.0	1.5	5.5
Distal median nerve (level 11)			
Case 1	66.7	33.3	0
Case 2	71.8	25.6	2.6
Control	93.0	3.5	3.5

* Normal appearance, axonal degeneration, and segmental demyelination and remyelination correspond to conditions A, conditions E, H, and conditions C, D, F, G, respectively, by the criteria described by Dyck *et al.* (1978).

TABLE 2. DISTRIBUTION OF AMYLOID DEPOSITS*

	Spinal cord parenchyma	*Subarachnoid and subpial space of the spinal cord*	*Ventral root (L4)*	*Dorsal root (L4)*	*Dorsal root ganglia (L4)*	*Spinal nerve*
Case 1	–	++	±	++	+++	++
Case 2	–	+ ~ ++	±	++	+++	++

	Sciatic nerve	*Tibial nerve*	*Sural nerve*	*Median nerve*		*Sympathetic ganglia (T7–8)*
				Proximal	*Distal*	
Case 1	+++	++	+	++ ~ +++	++	+++
Case 2	+++	++	+ ~ ++	++	++	+++

* Frequency of amyloid deposits was estimated on transverse sections stained with Congo red and antihuman TTR antibody: ± = slight; + = mild; ++ = moderate; +++ = severe.

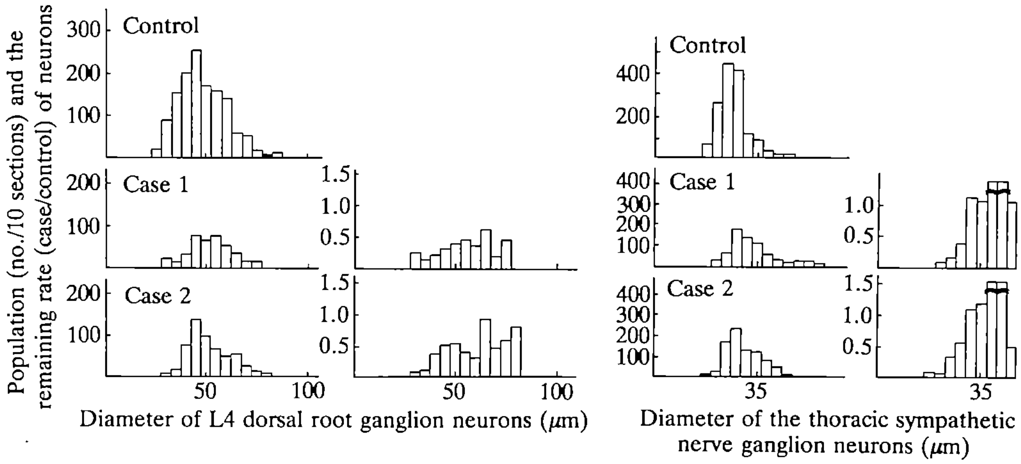


FIG. 7. Diameter-frequency histogram of the surviving dorsal root ganglion neurons (*left panels*) and sympathetic ganglion neurons (*right panels*) showing a severe depletion, with a greater loss of smaller neurons.

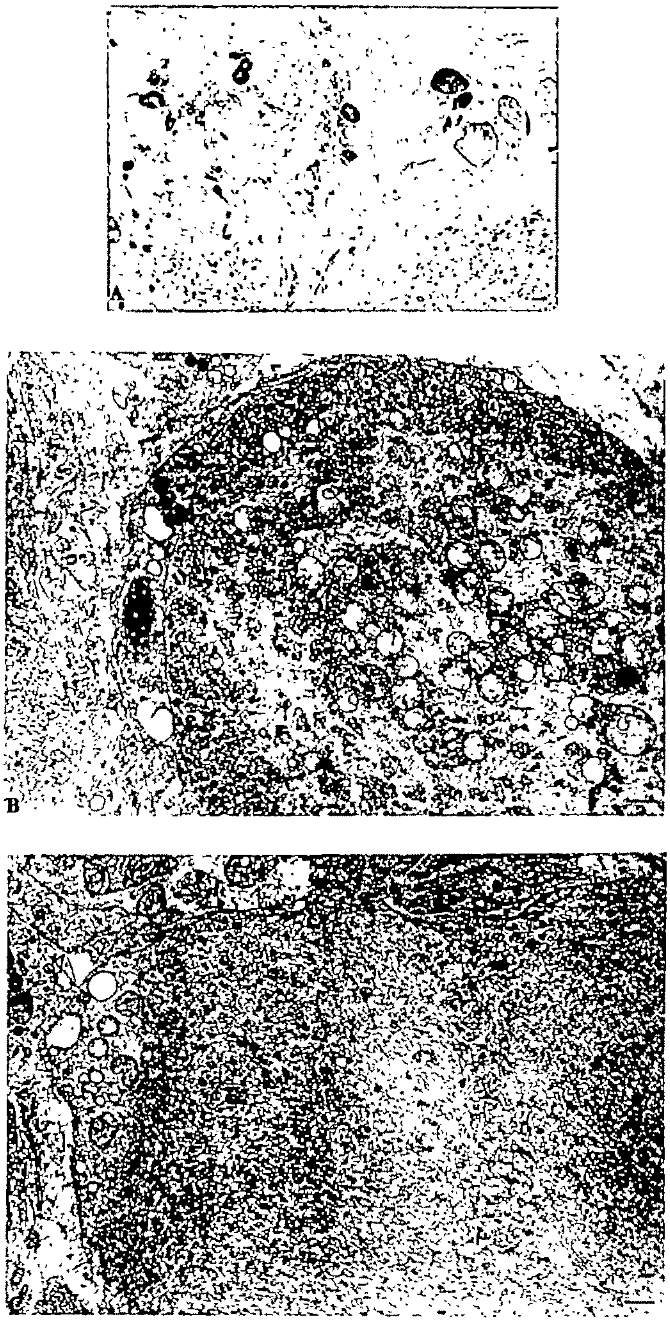


FIG. 8. Immunohistochemical and electron microscope photographs of dorsal root and sympathetic ganglia. A, transverse section of the L4 dorsal root ganglion (*Case 2*) stained with antiphosphorylated neurofilament antibody (Ta-51). Spheroids are strongly stained. Bar = 10 μm. B, large spheroid containing numerous cell organelles and neurofilaments. L4 dorsal root ganglion (*Case 1*). Bar = 1 μm. C, large spheroid containing a massive neurofilamentous aggregate with distorted cell organelles at its margin. Thoracic sympathetic ganglion (*Case 1*). Bar = 1 μm.

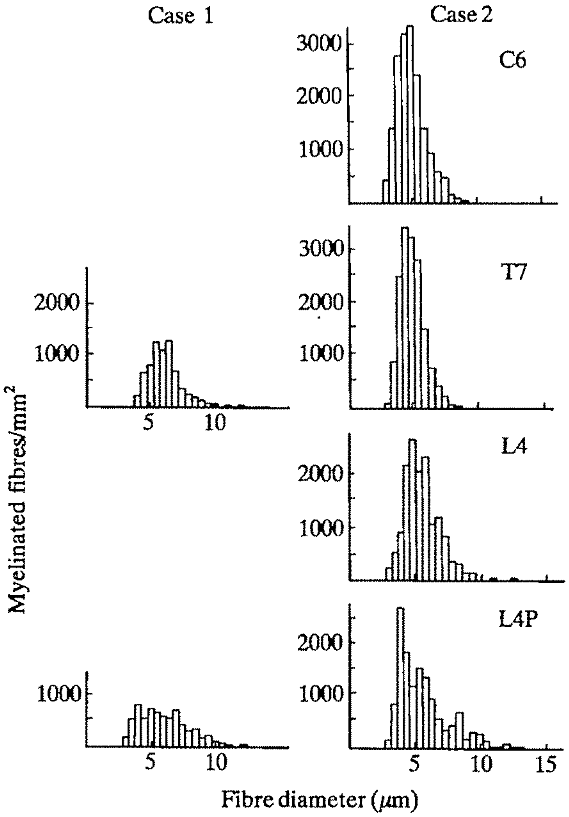


FIG. 9. Size-frequency histograms of the myelinated fibres in the L4 dorsal root (L4P) and the fasciculus gracilis at various levels (L4, T7, C6).

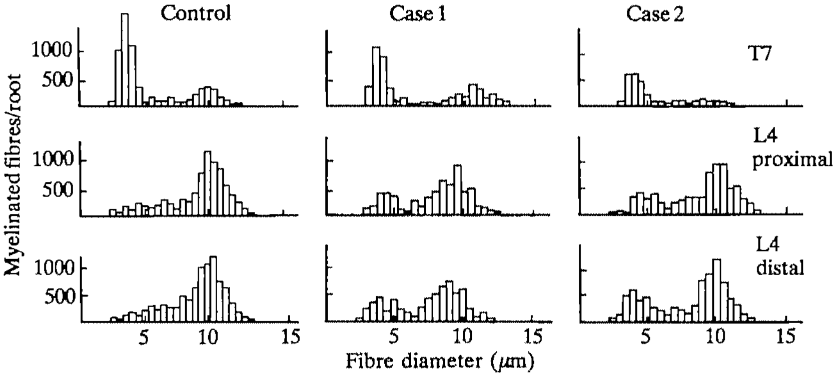


FIG. 10. Size-frequency histograms for myelinated fibres in the T7 and L4 ventral spinal roots.

The present study has indicated that small sensory and sympathetic neurons and unmyelinated fibres are preferentially involved in the primary process, but marked sprouting producing numerous small myelinated fibres may modify the observed fibre size distribution. Preferential loss of small sensory and sympathetic neurons will be the pathological background of the preferential loss of small myelinated and unmyelinated fibres. This may also support the view that much of the degeneration of peripheral nerves is the consequence of lesions in the dorsal root ganglia (Götze and Krücke, 1941; Krücke, 1959, 1963; Thomas and King, 1974).

Axonal sprouts were ubiquitous in both patients, but their occurrence was not universal throughout the nerves. Axonal sprouts were not prominent in the dorsal spinal roots, in spite of severe fibre loss, while in the ventral spinal roots and median nerves, axonal sprouts were significant. From previous reports on sural nerve biopsies, clusters of small fibres were not observed to be conspicuous, although they were illustrated by Thomas and King (1974). In severely affected nerves, newly regenerated axons may be reinvolved in the disease process, but the above-mentioned findings suggest that these sprouts may possibly be derived preferentially from motor axons, rather than from sensory or autonomic axons. Severe loss of the sympathetic and primary sensory neuronal cell bodies, with fairly good preservation of the motoneurons and their proximal axons, may support this view. These findings also correlate well with the predominant autonomic and sensory symptoms, and the less severe involvement in motor function in the clinical manifestations.

Our results confirmed that the presence of amyloid deposits is strongly linked to neuronal and axonal destruction, as previously reported (Dyck and Lambert, 1969; Shirabe *et al.*, 1973; Thomas and King, 1974; Horder and Treip, 1977; Sumino *et al.*, 1983; Yamada *et al.*, 1984). This is supported by the finding that the central processes of the primary sensory neurons remained intact after they entered the posterior columns where no amyloid deposits were present, while their numbers were reduced in the posterior roots where amyloid deposits were conspicuous. In addition, the motor neuron cell bodies and proximal axons were relatively well preserved, where amyloid deposits were few, but their axons were almost absent in the distal sciatic and tibial nerves where amyloid deposits were abundant. No particular parenchymal damage was seen in the CNS where no amyloid deposits were present.

The distribution of amyloid deposits, most evident in dorsal spinal roots and ganglia, peripheral nerves distal to the spinal nerves, and in sympathetic ganglia, and less conspicuous in the ventral spinal roots and absent in the CNS, also corresponded well to the distribution of a region of increased permeability of the blood-nerve and blood-brain barriers (Olsson, 1975). Recent studies (Seitz *et al.*, 1985; Mata *et al.*, 1987) have suggested that the blood-nerve barrier is more permeable than was previously believed, and is effective in slowing but not preventing the entry of large serum proteins into the endoneurial spaces. Sensory and sympathetic nerve ganglion cells and their axons are therefore constantly exposed to serum proteins, even in normal nerves (Mata *et al.*, 1987), and some serum proteins are now considered to have a role in normal axonal biology. The precise reason why abnormal TTR present in this disease remains soluble in the serum, but is precipitated in the endoneurial spaces, is not known. However, the parallel distribution of amyloid deposits and neuronal damage observed in this study suggests that the deposited amyloid fibrils may be harmful to the nerves rather than the abnormal soluble TTR itself.

Both Schwann and satellite cells were often surrounded by amyloid fibrils. Their basement membrane was frequently destroyed by these fibrils, an observation which is in agreement with previous reports (Takahashi *et al.*, 1974; Thomas and King, 1974; Said *et al.*, 1984), and this was also accompanied by distorted reactive Schwann cells and satellite cell processes. Collagen fibrils in the endoneurial space were also distorted by the invasion of amyloid fibrils. Normal Schwann cell-axon interactions are maintained when the Schwann cells are surrounded by collagen fibrils as well as by basement membrane (Bunge and Bunge, 1978), both of which were often distorted or destroyed in this neuropathy, affecting the normal alignment of Schwann cells, basal lamina and collagen fibrils. This morphological evidence may suggest that the Schwann and satellite cells are directly affected by the amyloid fibrils, and that this may induce the subsequent axonal and neuronal degeneration as a consequence of the disturbed axon-Schwann cell interactions (Bunge and Bunge, 1978).

Another possible cause of nerve fibre loss is ischaemia, as proposed by Kernohan and Woltman (1942), and recently by Hanyu *et al.* (1989). Although amyloid deposits are frequently associated with endoneurial vessels, obstructed vessels are rarely seen. The dorsal root ganglion neurons and dorsal roots are not as markedly involved in neuropathies of vasculitic origin, such as necrotizing vasculitis (Dyck *et al.*, 1972; G. Sobue *et al.*, unpublished observations). A multifocal distribution of myelinated fibre loss in the fasciculi of the proximal nerves of both present cases was mainly related to deposits of amyloid and was somewhat different in pattern to that observed in ischaemic neuropathy (Dyck *et al.*, 1972). The role of ischaemia in the pathogenesis of type I FAP still requires evaluation.

Direct compression of neurons and nerve fibres by amyloid deposits has been considered as a possible cause of this neuropathy (Dyck and Lambert, 1969; Thomas and King, 1974; Horder and Treip, 1977; Said *et al.*, 1984). In both present cases, similar findings were frequent, with direct compression of nerve fibres by amyloid. It is possible that direct compression of axons may induce axonal damage independent of Schwann cell dysfunction. This process may be relevant to the finding of a distally accentuated process, particularly distal dominant axonal degeneration and a proximal segmental process clustering to a single fibre, as observed in teased fibres in the present study as well as in that of Said *et al.* (1984). However, a direct connection between compression by amyloid and axonal and neuronal damage is not established morphologically and this requires elucidation in the future.

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MAPPING OF BRAINSTEM LESIONS BY THE COMBINED USE OF TESTS OF VISUALLY-INDUCED EYE MOVEMENTS

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SUMMARY

To determine the diagnostic value of visually-induced eye movements for indicating the lateralization of the lesion, optokinetic nystagmus (OKN), fixation-suppression of caloric nystagmus and pursuit eye movements were investigated in 28 patients who showed discrete unilateral brainstem lesions. In all patients, pursuit gains decreased in parallel with the direction of the impairment of slow-phase OKN velocity with a significant left/right difference. Decreases of gains were predominantly towards the affected side in 22 patients, whereas they were predominantly towards the contralateral side in 2 patients with dorsal tegmental pontine lesions and in 4 out of 8 patients with Wallenberg's syndrome. The relationship of pursuit gains to percentage reduction of fixation-suppression of caloric nystagmus (%FS) showed no correlation.

The following four groups were classified. In group A, which was the largest, pursuit gains and %FS decreased predominantly towards the lesioned side. This group consisted of 5 patients with lesions in the midbrain, 6 patients with lesions in the ventral pons and 4 out of 8 patients with Wallenberg's syndrome. The opposite of group A was group D, showing reverse electro-oculographic (EOG) patterns to those in group A in relation to the lesioned side. Group D consisted of 2 patients with lesions in the dorsal pontine tegmentum. This observation, taken together with the decreases of pursuit and OKN gains in relation to the lesioned side, might indicate that lesions of ascending fibres are responsible for pursuit and OKN abnormalities. Group B, consisting of 7 patients with lesions either in the superior or middle cerebellar peduncles, showed decreased pursuit gains predominantly towards the lesioned side and %FS reduced predominantly towards the side contralateral to the lesion. EOGs of these patients were consistent with the results of floccular ablation in the monkey. In group C, these two parameters showed patterns opposite to those in group B in relation to the lesioned side and this group consisted of the other 4 patients with Wallenberg's syndrome. In patients of this group, the inferior cerebellar peduncle might be involved. The combined use of these tests is thus useful for lateralizing the lesion in the brainstem.

INTRODUCTION

In primates, who have a pursuit system, the velocity of the slow-phase of optokinetic nystagmus (OKN) consists of two distinct components which respond to step changes in stimulus velocity: an initial rapid rise which is related to the transcortical-cerebellar route and is thought to reflect the engagement of smooth pursuit mechanisms and an additional slower rise of slow-phase OKN velocity that resembles OKN found in nonfoveal

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animals (Cohen *et al.*, 1977; Lisberger *et al.*, 1981; Zee *et al.*, 1981, 1987; Waespe *et al.*, 1983).

Recently, fragmented but definite evidence in the monkey has accumulated suggesting that cells of the nucleus of the optic tract (NOT) (Hoffmann *et al.*, 1988) and the medial dorsal pontine nucleus (MDPN) (Keller and Crandall, 1983) signal retinal slip during OKN and that cells in the dorsolateral pontine nucleus (DLPN) respond to movement of a small visual spot (Suzuki and Keller, 1984). Furthermore, lesions in either NOT or DLPN lead to selective OKN deficits (Kato *et al.*, 1988) or marked deficits in both initiation of pursuit and pursuit gains (May *et al.*, 1988).

Although extensive clinical studies have been carried out over the years, the question as to how pursuit and OKN behave in unilateral brainstem lesions remains unanswered. Fixation-suppression of caloric nystagmus, on the other hand, was introduced clinically by Hart (1967). The failure of fixation-suppression of caloric nystagmus has been proposed as indicating an infratentorial lesion, based on a survey of over 2000 patients (Coats, 1970). This observation has been confirmed (Dichgans *et al.*, 1978; Kato *et al.*, 1979) and extended by classifying patterns of pathological fixation-suppression into three types according to the results of an alternate hot and cold caloric test (Kato *et al.*, 1979). Neurophysiological studies later implicated the flocculus as the structure through which the visual system can alter or modify vestibular nystagmus (Ito *et al.*, 1974; Lisberger and Fuchs, 1974). Floccular ablation in the monkey resulted in pursuit deficits with subsequent loss of visual suppression of vestibular nystagmus (Takemori and Cohen, 1974) and OKN impairment in proportion to the reduction of the rapid rise in OKN velocity (Zee *et al.*, 1981; Waespe *et al.*, 1983). Furthermore, recent neurophysiological studies have disclosed that the flocculus receives visual signs from the pontine nuclei where cells are involved both in pursuit and OKN (Noda, 1981; Langer *et al.*, 1985). Thus viewed, OKN and fixation-suppression of caloric nystagmus seem to be closely related to pursuit eye movements.

In the present study, the diagnostic value of these tests in indicating the lesioned side was investigated in patients who showed discrete unilateral brainstem lesions, and the relationship of both OKN and fixation-suppression of caloric nystagmus in relation to pursuit eye movements is discussed from the neuroanatomical and neurophysiological points of view. Abnormalities in the fast-phase velocity in OKN have been reported elsewhere (Kanayama *et al.*, 1987).

MATERIAL AND METHODS

Out of a series of 2240 patients from 1979 to 1984 who visited the electro-oculography (EOG) laboratory and 32 patients who were admitted to the Neurosurgical Division, 28 patients were diagnosed as having discrete unilateral brainstem lesions based both on neurological signs and symptoms as well as CT findings. Wallenberg's syndrome was diagnosed only by neurological signs and symptoms. Lesions in the cerebellar peduncles were confirmed by cerebellar signs and on CT. Patients with internuclear ophthalmoplegia were excluded, because such eye conditions have marked effects on these visually-induced eye movements. Patients with bilateral brainstem lesions were also excluded.

Recording procedures

Electrodes (Ag-AgCl) (Nihon Kohden) were placed laterally in the outer canthus of each eye. A ground electrode was located on the forehead. Horizontal eye movements were recorded with direct current (d.c.) EOG (0–20 Hz; −3 dB) and rectified by amplifiers with a 0.03 s time constant to obtain the slow-phase velocity of nystagmus.

Test procedures

The test battery consisted of calibration, gaze test, position test for nystagmus in the supine, right and left side down, and head-hanging positions. The caloric test was carried out with patients in the horizontal position and with the horizontal semicircular canal lying in an optimal position. According to the method of Fitzgerald and Hallpike (1942) as modified by Otani (1962), the caloric stimulus was 50 ml water at temperatures of 30° and 44° C during an irrigation period of 20 s. An interval of about 7 min was allowed between each infusion. Patients received alternate hot and cold caloric stimulation. During the maximum intensity of slow-phase velocity, patients were requested to fix their gaze on a light spot 3 m away for 10 s. Thus the percentage reduction of slow-phase velocity induced by ocular fixation was calculated (Kato *et al.*, 1984). The caloric test was performed in all patients with eyes open in complete darkness. Mental arithmetic stimuli were provided to maintain mental alertness.

OKN was elicited by rotating stripes of light projected onto a white screen. Patients were surrounded by the large screen. OKN stripes (white 4°, black 26°) were rotated at an angular acceleration of 1.2 $\text{deg}\cdot\text{s}^{-1}$ for 100 s. Patients were exposed to two different stimuli applied in both a clockwise and a counter-clockwise direction.

Pursuit eye movements were induced with a luminous spot that moved in a sinusoidal curve at 0.3 Hz and the target velocity was monitored with a band-width of 0–3 Hz. The excursion of the target was ± 10° and the velocity could be varied from 0 to 18.8 $\text{deg}\cdot\text{s}^{-1}$. Smooth pursuit was tested with an illuminated stationary background.

Data analysis

Induced nystagmus was recorded on polygraph paper (Nihon Kohden), while the nystagmus data were directly computed through FM magnetic tape (net band-width, 1 kHz) which stored the nystagmus data for later additional computer analysis. The analog data of the eye positions obtained from d.c. EOG were digitized at a rate of 100 samples/s through a multichannel 12 bit analog-digital converter. Details of the on-line digital computer analysis techniques have been reported elsewhere (Kato *et al.*, 1984; Nakamura *et al.*, 1985, 1986).

The reduction of the slow-phase velocity of caloric nystagmus was calculated during the period of the first 5 s of 10 s of ocular fixation and compared with the slow-phase velocity during the period of a prefixation 5 s control. The amount of fixation-suppression of caloric nystagmus was equal to 1 − (slow-phase velocity in light/slow-phase velocity in dark) expressed as a percentage. The percentage reduction established with slow-phase velocity best distinguished normal from abnormal using a threshold of 60%. A reduction of less than 60% is considered to indicate pathological fixation-suppression (Kato *et al.*, 1984). Although patients received alternate hot and cold caloric stimulation, the percentage reduction of slow-phase velocity showed a similar tendency between hot and cold stimulation. Therefore, for the purposes of this paper the percentage reduction induced by hot stimulation was shown.

The increase of slow-phase OKN velocities in normal subjects was approximately the same as that of stimulus velocities up to 60 $\text{deg}\cdot\text{s}^{-1}$, while at stimulus velocities greater than 60 $\text{deg}\cdot\text{s}^{-1}$, the increase of slow-phase velocities tapered off (Nakamura *et al.*, 1986). In order to evaluate these relations in detail, the average gain (the ratio of slow-phase velocity and stimulus velocity) was measured as the average of each 5 $\text{deg}\cdot\text{s}^{-1}$ of stimulus velocity. At stimulus velocities of less than 60 $\text{deg}\cdot\text{s}^{-1}$, the average gain decreased slightly, but was more than 0.8. Therefore, to estimate slow-phase velocity quantitatively, the maximal stimulus velocity at which the gain of OKN velocity was more than 0.8, was termed as the 'optokinetic adaptation limit' (OAL). In normal subjects, the average value of OAL was

81.0 ± 11.7 deg·s^{-1} and the lowest value was 52.5 deg·s^{-1} and left/right differences of OAL values were within 10 deg·s^{-1} in all subjects without exception. Based on these data, left/right OAL differences greater than 10 deg·s^{-1} were judged as indicative of abnormal OKN velocity (Nakamura *et al.*, 1986).

Smooth pursuit was assessed by measuring eye velocity as the eye passed through the primary position. Saccadic eye movements were identified based on their characteristic velocity profile (Nakamura, 1985, 1986). After the saccades were identified and removed, the gaps in the remaining slow-phase eye velocity record were filled by connecting points on each side of the missing segment.

Pursuit gain was calculated (eye velocity/target velocity) and a mean obtained from 10 trials (Baloh *et al.*, 1976).

In all patients listed here who showed discrete unilateral brainstem lesions, values of the pursuit gains, OALs and percentage reduction of fixation-suppression of caloric nystagmus (%FS) were predominantly impaired on one side. Therefore, in order to investigate the relation of these parameters with regard to the lesioned side, the direction of pursuit eye movements and slow phase of OKN was designated according to the direction of the movement of stimulus and vestibular nystagmus, according to the slow phase of nystagmus. For ease of comparison, each parameter towards the lesioned side was subtracted from that towards the side contralateral to the lesion and the values subtracted were plotted and compared with each other between patient groups (*see* Table). The same case numbers are used in the text as in the Table.

TABLE. RELATIONSHIP BETWEEN LESION SITES AND EOG TESTS*

			Pursuit gain			*OAL (deg·s^{-1})*			*%FS*		
Lesion site	*Case*	*Side*	*R*	*L*	*Contra-Ipsi*	*CW*	*CCW*	*Contra-Ipsi*	*R*	*L*	*Contra-Ipsi*
Midbrain	1	R	0.54	0.85	0.31	25	60	35	0	62	62
	2	R	0.70	0.85	0.15	20	50	30	33	80	47
	3	R	0.45	0.65	0.20	15	45	30	40	65	25
	4	R	0.80	0.87	0.07	20	50	30	5	60	55
	5	L	0.80	0.45	0.35	50	10	40	60	16	44
Ventral pons	6	L	0.54	0.36	0.18	25	0	25	14	0	14
	7	R	0.85	0.90	0.05	35	55	20	50	71	21
	8	R	0.56	0.76	0.20	25	50	25	75	76	1
	9	R	0.33	0.70	0.37	0	40	40	36	41	5
	10	R	0.67	0.82	0.15	45	70	25	31	36	5
	11	L	0.98	0.80	0.18	70	50	20	56	53	3
Dorsal pons	12	L	0.68	0.92	−0.24	30	70	−40	25	76	−51
	13	L	0.75	0.95	−0.20	25	70	−45	0	69	−69
Wallenberg's syndrome	14	L	0.90	0.48	0.42	70	40	30	67	0	67
	15	R	0.75	0.87	0.12	20	50	30	8	63	55
	16	L	0.79	0.46	0.33	40	5	35	72	50	22
	17	L	0.97	0.80	0.17	55	20	35	70	52	18
	18	R	0.69	0.24	−0.45	35	0	−35	0	56	56
	19	R	0.91	0.51	−0.40	65	10	−55	0	79	79
	20	R	0.85	0.60	−0.25	70	10	−60	33	72	39
	21	L	0.83	0.98	−0.15	25	50	−25	70	0	70
Superior cerebellar peduncle	22	L	0.83	0.72	0.11	70	20	50	0	72	−72
Middle cerebellar peduncle	23	L	0.86	0.68	0.18	70	50	20	14	79	−65
	24	L	0.98	0.75	0.23	50	5	45	33	76	−43
	25	R	0.77	0.97	0.20	35	60	25	73	50	−23
	26	R	0.60	0.85	0.15	25	50	25	70	33	−37
	27	L	0.88	0.81	0.07	50	30	20	55	87	−32
	28	L	0.98	0.48	0.50	55	5	50	28	80	−52

* Patients with Wallenberg's syndrome separated into two subgroups, indicated by dotted line. Contra = contralateral; Ipsi = ipsilateral; OAL = optokinetic adaptation limit; CW = clockwise; CCW = counter-clockwise; FS = fixation-suppression.

CASE REPORTS

Patients with midbrain lesions

Case 1 was a 53-yr-old man who was admitted to the municipal hospital with a complaint of sudden attacks of vertigo, nausea, vomiting and unsteady gait. After 6 wks during which his symptoms and signs showed some improvement, he was admitted to the authors' institution for neuroradiological investigation. Examination showed nystagmus on lateral gaze to the left and minimal left facial weakness of central origin. He was a little unsteady on standing and tended to veer to the right. CT sections through the midbrain in this patient showed a low-density area in the right midbrain tegmentum (fig. 1). The EOG test revealed nystagmus on lateral gaze to the left and right. There was moderate spontaneous nystagmus to the left in darkness. Pursuit eye movements of this patient were slow and he needed catch-up saccades to keep up with the image of the target moving to both sides. Rightward pursuit gain was 0.54 and leftward gain, 0.85 (fig. 2).

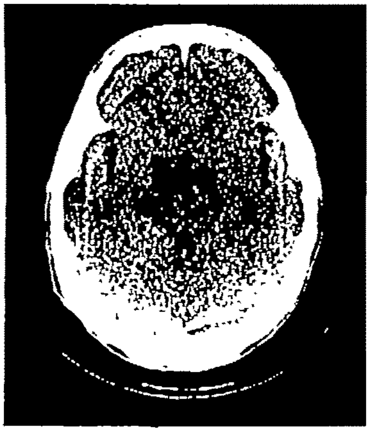

FIG. 1. CT section through the midbrain showing a low density area in the right tegmentum.

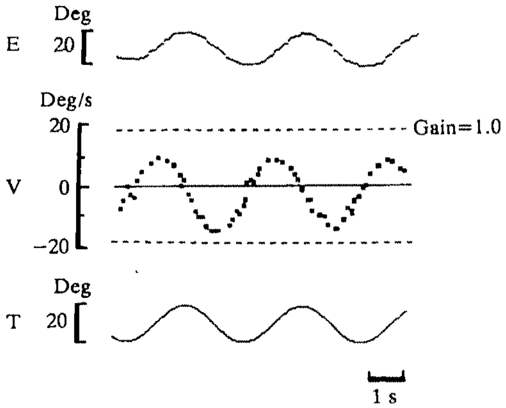

FIG. 2. Smooth pursuit to sinusoidally oscillating targets in the same patient as shown in fig. 1. Peak target velocity was 18.8 deg·s^{-1}. There was a predominant decrease in the rightward gain in the average eye velocity traces. Normal values (0.95 ± 0.07) are based on observations in our laboratory as well as those obtained by Baloh *et al.* (1976). E = eye position; V = eye velocities obtained from 10 cycles; T = target position.

Slow-phase OKN velocity to the right for this patient was saturated at stimulus velocities greater than 20 deg·s^{-1} and the OAL was 25 deg·s^{-1}, whereas the OAL on the left was 60 deg·s^{-1} and normal (fig. 3). %FS with a slow phase to the right was 0, whereas that to the left was 62% and normal (fig. 4). In this patient, the left/right difference in pursuit gains, OALs and %FS was 0.31, 35 deg·s^{-1} and 62%, respectively, showing a predominant decrease of these parameters toward the lesioned side (Table). All values in the Table were obtained as described above. The same was true with 2 other patients showing unilateral vascular lesions whether the lesion was located in the lateral (Case 2) or in the medial midbrain (Case 3) and with 2 remaining patients whose brainstem was occupied by a glioma extending from the thalamus to the midbrain (Cases 4 and 5). For ease of comparison, the relationship between pursuit gains and OALs, and pursuit gains and %FS is shown in figs 5 and 6, respectively. All values in the figures and elsewhere correspond to those in the Table. All 5 patients with lesions in the midbrain were classified into group A in figs 5 and 6 where values of these parameters decreased predominantly toward the lesioned side.

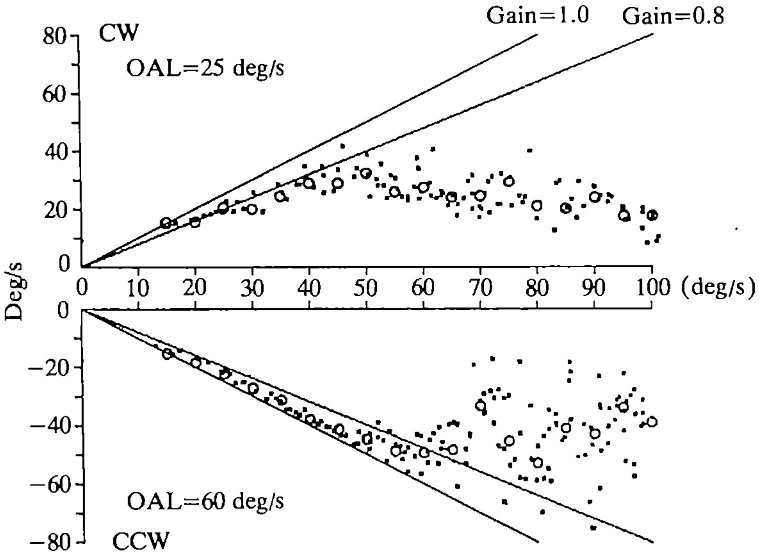

FIG. 3. Slow-phase OKN velocity of the same patient. *Upper* figure shows slow-phase OKN velocity to the right and the *lower*, that to the left. Ordinates indicate slow-phase velocity, abscissae, stimulus velocity and each dot, the slow-phase velocity corresponding to each stimulus velocity. Circles show the average gains as the average of each 5 deg·s^{-1}. CW = clockwise; CCW = counter-clockwise.

Cases with lesions in the ventral pons

The pursuit gains and OALs of this group showed distinct left/right difference, whereas the left/right difference in %FS was low, not showing any distinct difference. The maximal difference in the percentage reduction in this group was 21% (Case 7). In 5 other patients with similar lesions (Cases 6, 8, 9, 10, 11), the left/right difference in %FS was extremely low in contrast to that of other groups of patients (Table, group A, fig. 6). All parameters of these patients decreased predominantly toward the lesioned side (group A, figs 5, 6).

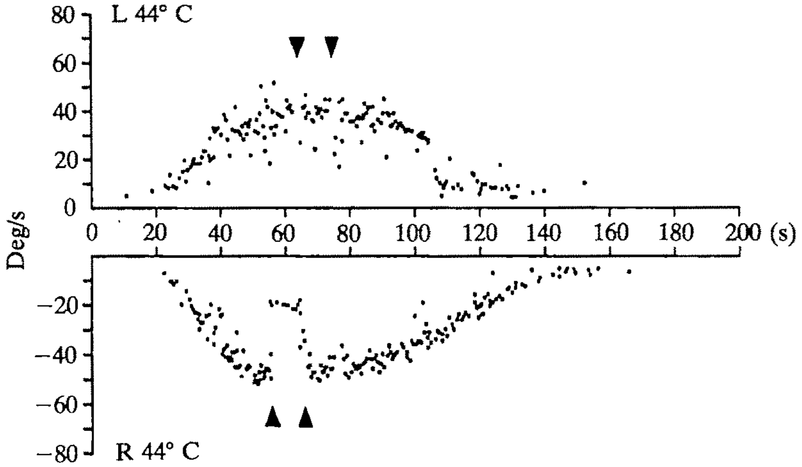

FIG. 4. Fixation-suppression of slow-phase velocity of caloric nystagmus. *Upper* figure shows rightward and the *lower* leftward slow-phase velocity. Vertical arrows indicate a period during fixation.

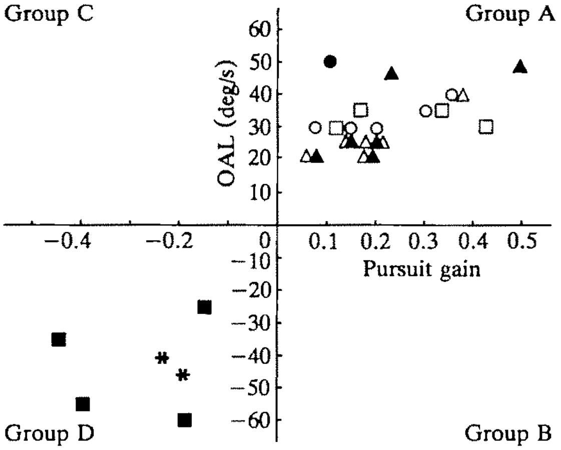

FIG. 5. The relationship between pursuit gains and OALs. All values in the figure and elsewhere correspond to those in the Table. Values of pursuit gains decreased in parallel with those of OALs. Correlation coefficient (r) = 0.75, $P < 0.001$. ○ = cases with lesions in the midbrain; △ = cases with ventral pontine lesions; * = cases with pontine lesions (dorsal); ● = a case with a lesion in the superior cerebellar peduncle; ▲ = cases with lesions in the middle cerebellar peduncle; □ = 4 cases of Wallenberg's syndrome; ■ = the other 4 cases of Wallenberg's syndrome. Patients in group A showed positive pursuit gains and OALs, i.e., decreases of these parameters predominantly towards the lesioned side; patients in group D showed negative pursuit gains and OALs, i.e., EOG patterns opposite to those in A.

Cases with lesions in the dorsal pontine tegmentum

In these 2 patients (Cases 12 and 13), the left/right differences in pursuit gains, OALs and %FS were negative respectively, showing decreases of these values predominantly towards the side contralateral to the lesion (Table, group D, figs 5, 6). Patients in groups A and D showed EOG patterns opposite to each other with regard to the lesioned side (figs 5, 6).

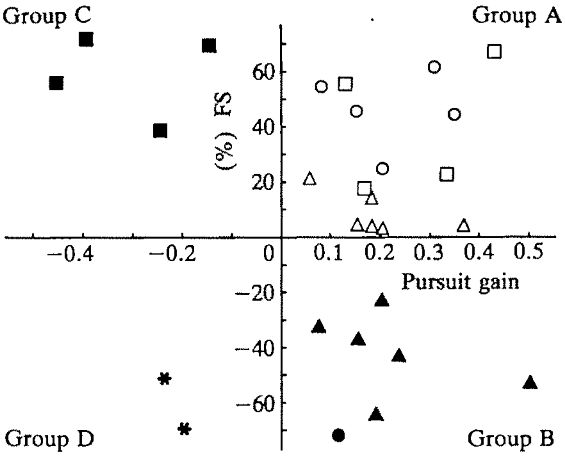

FIG. 6. The relationship between pursuit gains and %FS. The same symbols and specifications as in fig. 5. Patients in group A showed positive pursuit gains and %FS, i.e., decreases of pursuit gains and %FS predominantly towards the lesioned side; patients in group D showed negative pursuit gains and %FS, i.e., EOG patterns opposite to those in A. Patients in group B showed positive pursuit gains and negative %FS, i.e., decreases of pursuit gains predominantly towards the lesioned side and decreases of %FS predominantly towards the side contralateral to the lesion; patients in group C showed negative pursuit gains and positive %FS, i.e., EOG patterns opposite to those in B. Correlation coefficient (r) = −0.14.

Cases with lesions of the cerebellar peduncles

Case 22 was a 58-yr-old man who was admitted to a municipal hospital with the sudden onset of dysarthria and weakness of the left side, together with truncal ataxia. He had had diabetes mellitus and hypertension for several years. Examination showed conjugate eye deviation to the right and nystagmus on lateral gaze to the left and right, that to the left being coarse. Speech was slow and slightly dysarthric. In the upper limbs, finger-nose ataxia was more marked on the left, with rebound phenomenon and dysdiadochokinesis. In the lower limbs muscular tone was normal and power was unimpaired but coordination was impaired to a great extent on the left.

CT through the midbrain disclosed a spotty high density area at the superior cerebellar peduncle on the left (fig. 7).

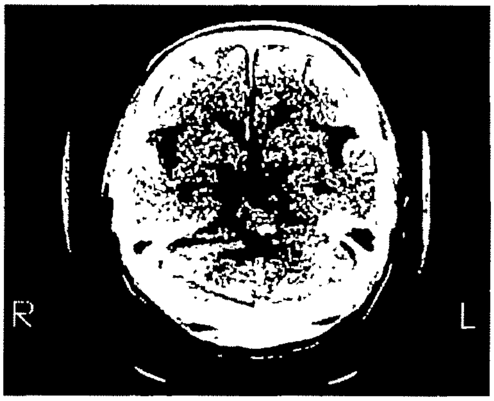

FIG. 7. CT section through the midbrain. A patchy high-density area is demonstrated in the superior cerebellar peduncle on the left.

EOG 2 wks after the onset of his attack showed gaze nystagmus in both directions, that to the left being coarse. There was moderate spontaneous nystagmus to the left in the dark. The left/right differences in pursuit gains and OALs was 0.11 and 50 deg$\cdot$s^{-1}, respectively, showing a predominant decrease towards the lesioned side (group A, fig. 5), whereas the left/right difference in %FS was −72%, showing a predominant decrease towards the side contralateral to the lesion (group B, fig. 6) The same was true with patients showing lesions in the middle cerebellar peduncle (Cases 23, 24, 25, 26, 27, 28; Table, group B, fig. 6).

Lateral medullary syndrome

Eight patients with Wallenberg's syndrome clearly diverged into two different subgroups based on the EOG test (Table). In the 4 patients (Cases 14, 15, 16, 17), the left/right differences in pursuit gains, OALs and %FS were all positive, showing a predominant decrease of these parameters towards the lesioned side (group A, figs 5, 6). In the other 4 patients (Cases 18, 19, 20, 21), the left/right differences in pursuit gains and OALs were negative, showing a predominant decrease of these parameters towards the side contralateral to the lesion (group D, fig. 5), whereas the left/right differences in %FS were positive, showing a predominant decrease towards the lesioned side (group C, fig. 6). Test results did not indicate conversion of patients from one group to another. The latter subgroup of patients with Wallenberg's syndrome showed EOG patterns opposite to those of patients with lesions in the cerebellar peduncle (groups B, C, fig 6).

DISCUSSION

In all 5 patients with lesions in the midbrain, all 6 patients with lesions in the ventral pons and 4 out of 8 patients with Wallenberg's syndrome, pursuit gains, OALs and %FS decreased predominantly toward the lesioned side. This suggests that the neuronal substrates responsible for these eye movements share a common pathway in part or descend in close relation with each other in the brainstem. This speculation has been supported by neuroanatomical data in the monkey showing that pretectofugal fibres from the NOT are ipsilateral to the medial pons (T. Ikarashi, K. Harada and I. Kato, unpublished) and corticofugal fibres responsible for pursuit descend through the cerebral peduncle dorsolaterally to the basilar pons (Ungerleider *et al.*, 1984).

In patients with lesions in the basilar pons, OALs of slow-phase OKN velocity were impaired proportionally to decreases of pursuit gains; %FS, however, did not show a clear left/right difference in proportion to decreases of pursuit gains.

Recent studies have disclosed that the frontal eye fields, the areas within the middle temporal sulcus, and the posterior parietal cortex participate in the generation of pursuit in the normal monkey (Kawano *et al.*, 1984; Bruce *et al.*, 1985; Newsome *et al.*, 1985). Furthermore, these regions project to the DLPN (Ungerleider *et al.*, 1984), where units related to pursuit eye movements have been demonstrated (Suzuki and Keller, 1984; May *et al.*, 1988). Units related to OKN are located in the MDPN ventral to the nucleus reticularis tegmenti pontis (Keller and Crandall, 1983), showing a completely different cell population. The discrepancy between %FS and pursuit gains shown in group A, fig. 6 could possibly be ascribed to lesions partly involving both afferent and efferent fibres of the DLPN, extending into the MDPN. However, it seems premature to speculate as to how the lesions demonstrated on CT partially interrupt the pathways suggested by the anatomical and the physiological data. This problem remains to be solved by future experiments.

In both patients with lesions in the dorsal tegmentum of the pons, pursuit gains, OALs, and the %FS decreased predominantly towards the side contralateral to the lesion, in contrast to patients in group A in figs 5 and 6.

Neuroanatomical studies in the monkey using tracing techniques showed that neither discernible fibres of passage nor relay nuclei are recognized in the dorsal tegmentum of the brainstem on the way to the pontine nuclei where nuclear cells are involved in OKN and pursuit (Ungerleider *et al.*, 1984; T. Ikarashi, K. Harada and I. Kato, unpublished). On the basis of the above anatomical evidence, there seems to be a sound basis for speculation that EOGs in patients with lesions in the dorsal tegmentum of the pons may result from lesions that affect ascending fibres mediating pursuit and OKN signals.

In cases with lesions in either the superior or middle cerebellar peduncles, pursuit gains and OALs decreased predominantly toward the side of the lesion, whereas %FS decreased predominantly towards the contralateral side, in contrast to EOG findings of cases with lesions in the midbrain, pons and 4 of the cases with Wallenberg's syndrome. The EOG findings that followed lesions in the cerebellar peduncles could best be interpreted as indicating a disturbance of the neuronal events of the flocculus, based on observations in the monkey (Waespe and Henn, 1981), and are also compatible with the EOGs of hemicerebellectomized monkeys (Westheimer and Blair, 1974; Takemori and Cohen, 1974) and with those of patients with cerebellar lesions (Dichgans *et al.*, 1978; Sato *et al.*, 1980).

In a previous publication, the authors reported findings for patients with well-defined cerebellar lesions on one side when seeking EOG abnormalities corresponding to those observed in hemicerebellectomized animals (Kato *et al.*, 1982). However, the cerebellar lesions, whether infarctions or haemorrhages, were large enough to occupy the cerebellar hemisphere (Kato *et al.*, 1986). Such patients, in terms of EOG abnormalities, showed pursuit deficits, OKN impairment from the lower stimulus ranges and failure of fixation-suppression of caloric nystagmus on both sides. Consequently, it can be emphasized that EOG abnormalities shown in group B, fig. 6 are solely ascribable to lesions either of the superior or the middle cerebellar peduncles. In view of the fact that the middle cerebellar peduncle is composed almost exclusively of the axons from the secondary neurons of the extensive corticopontocerebellar pathway while the superior cerebellar peduncle is composed of the great majority of fibres leaving the cerebellum (Williams *et al.*, 1989), it may be possible to show different EOG findings for lesions of these two peduncles. Nevertheless, EOG abnormalities using pursuit, OKN and fixation-suppression of caloric nystagmus as methods were identical. This is a matter for future investigation.

The 8 patients with Wallenberg's syndrome in the present study were clearly classifiable into two subgroups. From the neurological point of view, no differences between the two subgroups were detectable. In another report, pursuit, slow-phase OKN velocity and VOR-FIX (cancellation) gains were higher when they were in the direction of the slow phase of spontaneous nystagmus, that is, towards the side of the lesion (Baloh *et al.*, 1981), their pursuit gains and OALs being inconsistent with those of the top

4 cases in the present data (Table). In a subsequent study, we have not encountered any other type of Wallenberg's syndrome. The relation of pursuit gains and OALs with respect to %FS in the second Wallenberg's syndrome subgroup (Cases 18–21) showed EOG patterns opposite to those seen in patients wtih lesions in the cerebellar peduncles.

The zone of infarction in Wallenberg's syndrome is wedge-shaped, extending dorsally and medially from the lateral medullary surface immediately behind the olive to approach the floor of the fourth ventricle. Among nuclei and fibres of passage involved are the medial and descending vestibular nuclei, medullary reticular nuclei, restiform body and the spinocerebellar tract, structures known to be important for oculomotor control. The olive is slightly involved in nearly all cases, whereas the inferior cerebellar peduncle may be involved or spared (Fisher *et al.*, 1961). If speculation be permitted, the EOG pattern in the second Wallenberg's syndrome subgroup might result from the involvement of the inferior cerebellar peduncle.

A tentative diagram illustrating OKN and pursuit based on anatomical and physiological data of monkeys is shown in fig. 8.

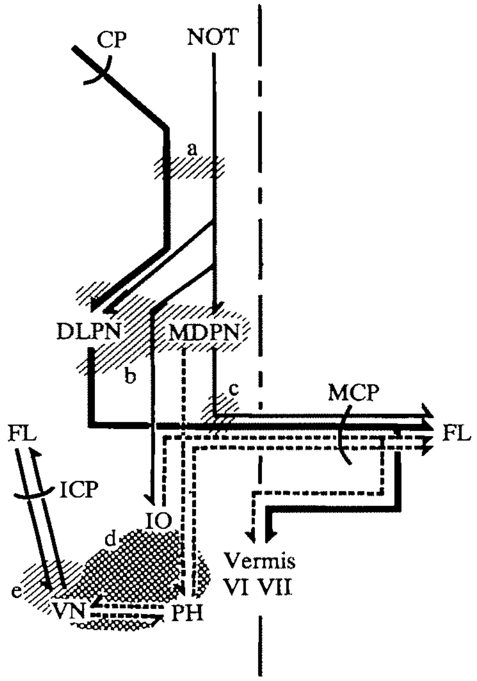

FIG. 8. A tentative diagram for OKN and pursuit. Thick lines = pursuit pathways, thin lines = OKN pathways, dotted lines = tracts not confirmed physiologically or anatomically, broken line = midline. a, midbrain lesions; b, ventral pontine lesions; c, lesions in the middle cerebellar peduncle; d, Wallenberg's syndrome (first subgroup); e, Wallenberg's syndrome (second subgroup). NOT = nucleus of optic tract; CP = cerebral peduncle; MDPN = medial dorsal pontine nucleus; DLPN = dorsolateral pontine nucleus; MCP = middle cerebellar peduncle; FL = flocculus; IO = inferior olive, dorsal cap; PH = nucleus prepositus hypoglossi; VN = vestibular nucleus; ICP = inferior cerebellar peduncle.

Relationship of OKN and fixation-suppression of VOR to pursuit eye movements

Pursuit gains in the present experiment decreased in parallel with the direction of the impairment of slow-phase OKN velocity, showing a close relation between them ($P < 0.01$). This is compatible with other clinical data (Zee *et al.*, 1976; Baloh *et al.*, 1986; Magnusson *et al.*, 1986) and supports the hypothesis that the slow phase of OKN may reflect the contribution of the pursuit system (Robinson, 1981).

Cancellation of the vestibulo-ocular reflex (VOR) which was referred to here as the fixation-suppression of caloric nystagmus, on the other hand, is generally believed to be due to the vestibular command being cancelled by equal and opposite command signals generated by smooth pursuit (Dichgans *et al.*, 1978; Tomlinson and Robinson, 1981). There is much evidence to support the idea that cancellation is performed by pursuit (Barnes *et al.*, 1978; Dichgans *et al.*, 1978; Halmagyi and Gresty, 1979). If the pursuit system actually participates in cancellation of VOR, the EOGs in patients with lesions in the cerebellar peduncles and in those in the second Wallenberg's syndrome subgroup, showing that the direction of the decrease of pursuit gains and %FS can be dissociated from each other might lend support to the hypothesis of a pursuit-cancellation relationship. However, the EOGs in 17 out of our 28 patients showed that the decrease of pursuit gains and %FS were predominantly in the same direction and offer no support for the idea that cancellation is also performed by the pursuit system. The relationship between them, in fact, proved to be insignificant (fig. 6).

From the results of other clinical observations, patients with cerebellar lesions showed a similar EOG pattern as in the present cases with involvement of the cerebellar peduncles (Dichgans *et al.*, 1978; Sato *et al.*, 1980). Patients with brainstem lesions involving the pontine reticular formation, however, showed impaired OKN reponses with a quick phase towards the ipsilateral side, and decreased fixation-suppression of vestibular nystagmus towards the contralateral side (Dichgans *et al.*, 1978), consistent with the EOG patterns in our second group of patients with Wallenberg's syndrome. At present, we have no information for or against suggestions as so far no reports have described the relationship of abnormal pursuit associated with abnormal cancellation of VOR to a precise brainstem lesion, although many papers have claimed that impaired pursuit eye movements also interfere with the slow-phase OKN velocity and the ability to cancel VOR (Zee *et al.*, 1976; Dichgans *et al.*, 1978; Halmagyi and Gresty, 1979; Baloh *et al.*, 1986).

On the basis of neuronal activities in the monkey, firing rates in some flocculus Purkinje cells increase in phase with eye velocity during smooth pursuit eye movements and almost all identical cells are modulated towards the same side as pursuit eye movements during cancellation of VOR (Miles and Fuller, 1975; Lisberger and Fuchs, 1978), which is consistent with another experiment on the flocculus, showing an increase in firing rates during conflicting visual-vestibular stimulation with suppression of the contralateral slow phase of vestibular nystagmus (Waespe and Henn, 1981). Decreased pursuit gain predominantly towards the lesioned side (Westheimer and Blair, 1974) and loss of visual suppression, with the slow phase towards the side contralateral to the lesion, could be interpreted as indicating a disturbance of the neuronal events of the flocculus (Takemori and Cohen, 1974). Firing rates in DLPN in the monkey, on the other hand, also increase in phase with the eye velocity (Suzuki and Keller, 1984), and chemical lesions in this region lead to predominant decreases of pursuit gains towards the lesioned side. However, VOR cancellation has not been investigated (May *et al.*, 1988). At present, we have no data to warrant further discussion. To what extent and in what way the pursuit system may participate in cancellation of VOR requires further investigation.

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EFFECTS OF ANTERIOR CORPUS CALLOSUM SECTION ON CORTICAL GLUCOSE UTILIZATION IN BABOONS

A SEQUENTIAL POSITRON EMISSION TOMOGRAPHY STUDY

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SUMMARY

Cortical glucose utilization was measured under light anaesthesia using positron emission tomography and ^{18}F-fluorodeoxyglucose before and serially after stereotaxic anterior corpus callosum section in 3 adult baboons (Papio papio); in 1 animal needles were introduced but callosotomy was not performed ('sham' operation). Lesion efficacy was verified by x-ray computerized tomography and by postmortem examination which indicated effective anterior two-thirds callosal section in all 3 baboons, as well as a small contusional area in the medial frontal cortex. A two-way layout analysis of variance performed on the regional cerebral metabolic rate of glucose (CMRGlc) data obtained in the frontotemporal, temporal and occipital areas revealed significant effects for both the time and the region factors ($P < 0.00001$ for each); the time effects indicated a significant initial metabolic depression ($P < 0.01$) at day 11 and 18, and a subsequent recovery ($P < 0.01$ to 0.05) at day 98. Average CMRGlc changes from preoperative values at successive studies were −23%, −27%, −17%, −8% and +2%, and −17%, −21%, −10%, −5% and +6% in the 'surgically approached' and the contralateral frontotemporal area, respectively. The frontotemporal/occipital CMRGlc ratio was significantly depressed at days 11, 18 and 32 ($P < 0.01$, 0.01 and 0.05, respectively), indicating a transient postoperative alteration in the cortical metabolic pattern. In the 'sham' animal, surgery induced negligible metabolic effects. Our results indicate that effective anterior corpus callosum section induces a transient bilateral depression of cortical metabolism, which predominates in the anterior parts of the brain, while metabolic recovery suggests efficient neuronal adaptation. These functional effects in the cortex may underlie the transient behavioural changes that follow anterior callosotomy in man.

INTRODUCTION

Despite numerous anatomical (Innocenti, 1986), neurophysiological (Innocenti, 1986; Wada, 1987) and neuropsychological (Gazzaniga, 1987) studies, the functions of the corpus callosum remain for a large part unknown. Observations from human and animal 'split-brain' studies have revealed that this major interhemispheric connection is essential

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to integrate sensory and motor performances of the two hemispheres (Innocenti, 1986; Gazzaniga, 1987). However, in man, corpus callosum section—an effective procedure to alleviate medically intractable epilepsy—or other surgical procedures induce temporary untoward behavioural effects (especially mutism) that are poorly understood (Oepen *et al.*, 1988; Purves *et al.*, 1988; Spencer, 1988). After unilateral brain lesions or strokes, transcallosal inhibition of cortical function has long been suggested as one mechanism for initial clinical effects and subsequent recovery ('transcallosal diaschisis', Kempinsky, 1958; Feeney and Baron, 1986). Positron emission tomography (PET) studies have shown a significant but transient reduction of *contralateral* cortical glucose utilization following unilateral thalamic strokes in man (Baron *et al.*, 1986) or electrolytic lesions of the nucleus basalis of Meynert in baboons (Kiyosawa *et al.*, 1987, 1989), in the mechanisms of which the corpus callosum probably plays a role. Because there is no published work on the effects of experimental callosal section on cerebral glucose metabolism, we embarked on such a study in baboons using PET with the aim of obtaining further insight into these questions.

The unique capability of PET to perform sequential observations using each animal as its own control was used here; despite the inevitably small sample of available animals, this sequential approach provides powerful data set for statistical evaluation of the effects of the lesion, while permitting the simultaneous investigation of their time course in the same animal and their correlation with the postmortem extent of the lesion.

MATERIAL AND METHODS

Animals

Four male baboons (Papio papio), weighing 6–9 kg were entered in the protocol, 3 of them for stereotaxic corpus callosum section and the fourth for 'sham' operation only.

Callosal section was performed under pentobarbital anaesthesia (15 mg/kg) with a small craniotomy. The technical details have been slightly modified from the initial description (Magni *et al.*, 1960; Fukuda *et al.*, 1988). Briefly, two small burr holes were made anteriorly and posteriorly, near the midline, slightly lateral to the superior sagittal sinus (right side for 2 baboons and left for the other); through these two burr holes, the dura mater was opened for a few millimeters. A fine solder wire bearing a thread attached to one end was inserted into one of the dural slits, and moved gently toward the other slit in order to bring it out of the skull. The thread was then introduced through the eye of 2 sewing needles attached to a stereotaxic apparatus. The needles were introduced gradually in stereotaxic conditions at the appropriate position, determined from the stereotaxic atlas for baboons (Riche *et al.*, 1968). After confirmation of the position using lateral and anteroposterior skull x-rays, the thread running loose between the two needles was tightened so as to cut down through the corpus callosum.

The 'sham' operation was performed as follows. After cutting the dura slightly left of the sagittal sinus, the needles to which the thread was similarly manipulated were introduced 10 mm higher than the usual position, and the thread tightened. It was then removed and the two needles were depressed to their usual position. In order to verify specific and nonspecific changes due to the operation, unenhanced x-ray axial computerized tomography (CT) of the brain was performed in each of the 4 baboons within 1 to 3 wks of surgery, using a CGE-CE9000 scanner with a slice thickness of 2 mm (except in baboon 3, 5 mm) under appropriate current and voltage (72 mA and 130 kV); the CT scan images were obtained in planes parallel to the orbitomeatal (OM) line, the animal being positioned as for the PET study and with the same head-holder.

At the end of the experimental protocol, the animal was deeply anaesthetized by ketamine (10 mg/kg) and injected with saturated KCl. The brain was removed immediately and fixed in 10% formalin for 3–4 wks. After 4–6 wks, the extent of the corpus callosum section and its related changes were verified, under optical microscope, on serial coronal paraffin sections stained with cresyl violet.

PET study

The cerebral metabolic rate of glucose (CMRGlc) was measured using the ECAT-II single slice PET device and the ^{18}F-fluorodeoxyglucose (FDG) technique before, and 11, 18, 32, 56 and 98 days after, the surgical intervention. The PET studies were performed according to our previously published protocol (Kiyosawa *et al.*, 1987, 1989). The baboons were lightly anaesthetized (EEG stages I or II) by an i.v. infusion of phencyclidine (7 μg/kg·min) supplemented by N_2O and O_2 (66–33%), curarized with alcuronium and artificially ventilated. This anaesthetic regimen is known to induce no appreciable effects on energy metabolism in the baboon neocortex but nevertheless prevents any stress effect (Fitch *et al.*, 1978). A catheter was inserted percutaneously into the femoral artery through which arterial blood was sampled for measurement of blood gases, pH, glucose concentration and radioactivities, and for monitoring of blood pressure. The end-tidal pCO_2 was monitored from the tracheal tube using the Beckman LB-2 analyser. The EEG and ECG were also recorded continuously. The central body temperature was kept within normal ranges using a homeostatic heating blanket. The ventilation rate and volume were adjusted so as to keep arterial pCO_2 and pH within normal ranges. According to fixed predetermined levels, adjusted using a postmortem atlas of the baboon brain produced especially for use in PET scanning (Riche *et al.*, 1988), the animal's head was carefully positioned in the PET camera by means of a specially designed head-holder equipped with ear-bars and a submandibular orientatable plastic frame such that the scan slices were parallel to the OM line, as verified by laser beams; this method also ensured reproducible positioning at follow-up studies.

Following i.v. injection of 2.6–7.4 mCi of FDG as a slow bolus, serial PET scanning was performed at the OM +15 mm level in order to get 12 'dynamic' images (midtime of last scan: 56 min); subsequently, 'static' scanning was obtained at the OM +5, +10 and +20 mm levels. The average FDG kinetic rate constants (k^*_1, k^*_2 and k^*_3) were estimated within 1.7 cm^2 circular region of interest (ROI) set on the right and left frontotemporal area of the OM +15 mm level by means of the method described previously (Mazoyer *et al.*, 1986), which uses the set of 12 serial images and the plasma ^{18}FDG curve. In the above calculation, k^*_4 was assumed as zero because its effects are negligible within the time-frame of the present study (Nelson *et al.*, 1985). Using appropriate k^*_i values (*see* Results), the 'autoradiographic' operational equation derived by Sokoloff *et al.* (1977) and Phelps *et al.* (1979) was applied so as to produce quantitative metabolic maps of the brain, 1 for each of the 4 levels studied. The values for regional CMRGlc (in mg/100 g·min) were obtained using 1.7 cm^2 (3.2 cm^3) circular ROIs set in the frontotemporal (OM +15 mm), the temporal (OM +10 mm) and the occipital (OM +15 mm) areas, where both CT scanning and postmortem study showed intact brain tissue, but excluding the frontal area (*see* below). The position of the ROIs was based on the anatomical atlas for use in PET studies developed by Riche *et al.* (1988); the ROIs so defined sampled a mixture of gray and white matter as a result of the partial volume effect (*see* Kiyosawa *et al.*, 1989, for discussion). Statistical analysis on CMRGlc data was made using the two-way layout analysis of variance (ANOVA) with two fixed factors (time and region). Individual mean values were compared with each other using the Newman-Keuls procedure (Winer, 1971).

RESULTS

General information

Following surgery, none of the baboons showed hemiparesis or overt behavioural abnormality. They were fully alert and showed normal appetite the day after operation. The body weight remained stable until the time of sacrifice except for 1 baboon (No. 3),

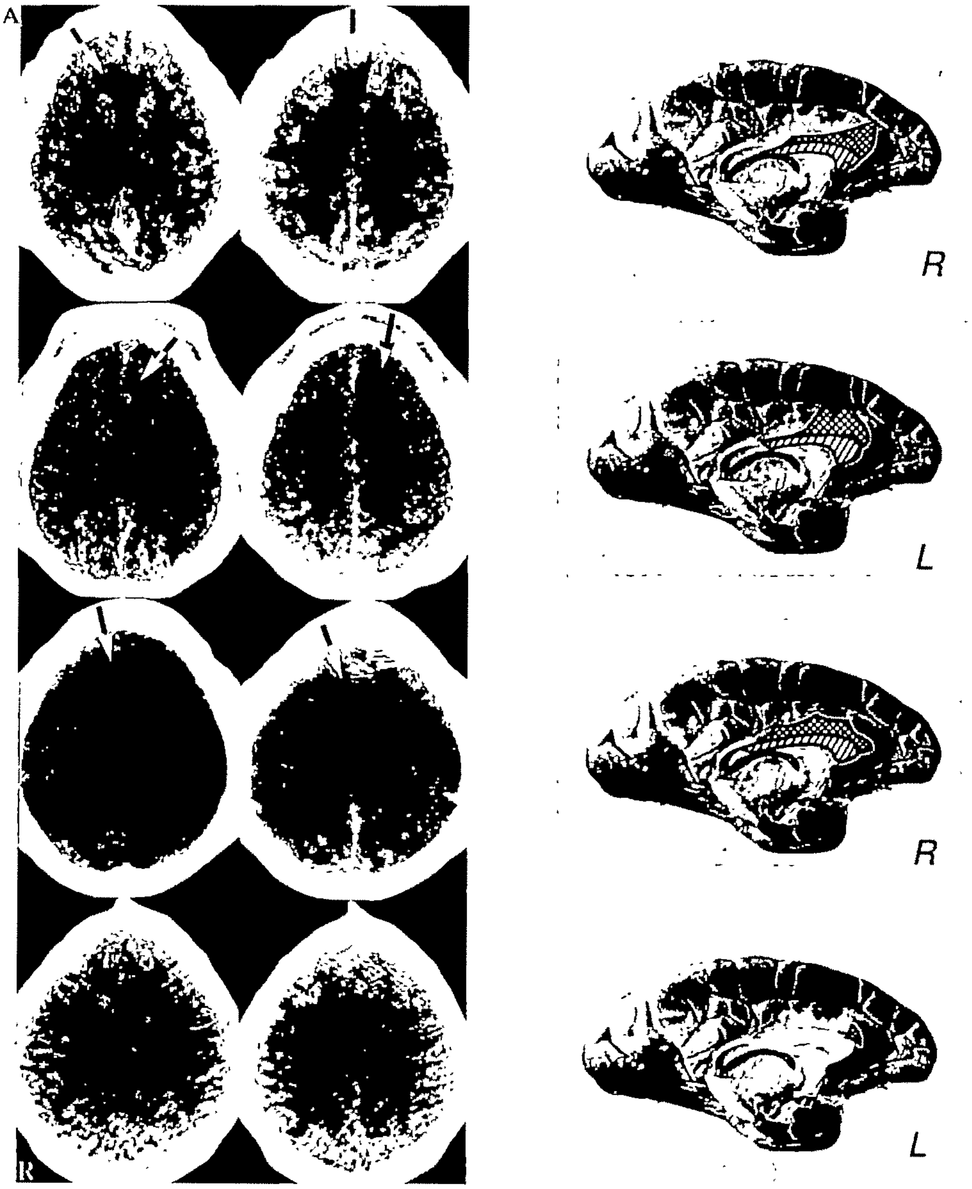

FIG. 1. A, unenhanced x-ray axial computerized tomography (CT) scans performed 17, 3, 10 and 12 days after surgery in operated baboons nos 1, 2 and 3 (3 upper pairs of scans, respectively), and in the 'sham' animal (lowest pair). The images obtained at the OM +15 mm and OM +20 mm are shown. R = right side. A small collection of blood in the subarachnoid space is apparent. An area of hypodensity was present in baboons 1, 2 and 3 anterior and superior to the frontal horn of the lateral ventricle on the surgically approached side (shown with white arrows) indicating effective anterior callosotomy with medial frontal contusional damage. Such changes were not readily apparent in the sham-operated animal. (Images in baboon 3 appear blurred because thicker CT scan slices were obtained; *see* text). B, the extent of the corpus callosum section (hatched area) and other surgically related changes on the medial side of the 'surgically approached' hemisphere (cross-hatched area), as determined by histological sectioning. The brain was obtained for postmortem studies at 201, 266, 182 and 68 days after surgery in baboons 1, 2 and 3, and in the 'sham' animal, respectively. R = right side; L = left side.

in whom an unexplained 20% loss occurred. Fig. 1 illustrates postoperative CT findings and the reconstructed extent of the corpus callosum section and related changes as determined postmortem in each baboon. CT showed a minor subarachnoid haemorrhage in the interhemispheric fissure. Around the anterior part of the corpus callosum and on the surgically approached side, a low density area was found in the 3 baboons with callosal section, which seemed to extend slightly to the medial aspect of the frontal lobe, but no definite alteration in density was shown in the 'sham' animal. Postmortem studies showed effective partial anterior (*see* fig. 1) callosotomy in each of the 3 operated baboons (approximately 2/3, 2/3 and 3/4 of the structure in baboons 1, 2 and 3, respectively), and a small contusional damage in the medial aspect of the surgically approached frontal lobe, particularly in the cingulate gyrus, in all 4 baboons, including the 'sham'-operated animals, although here this unwanted lesion was particularly small. The depth of this extracallosal lesion was less than 3 mm in each animal. No infarction was found.

PET results

Two of the 15 postcallosal section studies (both in baboon 3, day 56 and 98) were disregarded because of technical errors (completely wrong head positioning due to breakdown of the laser system of the PET camera in one study, and grossly inappropriate anaesthesia during the PET scanning in the other); a late, initially unplanned PET study could, however, be performed at day 207 in this animal to obtain some information on time course. One postoperative study (day 56) in the sham-operated animal could not be performed because of personnel problems. Thus, in spite of our attempt at planning a completely factorial design, the full data set in each time sequence (i.e., 3 baboons ×6 studies) could not be obtained.

k^*_i values. These values (frontotemporal area) before and after operation are shown in Table 1, together with the values previously determined in our institute in 7 Papio anubis baboons in the control state, using exactly the same physiological conditions (Kiyosawa *et al.*, 1989). A two-tailed Student's t test showed no significant difference between these previous and the present control data. The one-way layout ANOVA also showed no significant difference in k^*_i values within the time sequence in the present animals, and plasma glucose concentration was essentially constant and within normal ranges at all times (Table 1). Thus the subsequent CMRGlc calculation using the 'in vivo autoradiographic' method of Phelps *et al.* (1979) employed the standard previously used set of k^*_i values ($k^*_1 = 0.086$, $k^*_2 = 0.116$, $k^*_3 = 0.0499$; *see* Table 1) and a lumped constant of 0.42 (Kiyosawa *et al.*, 1989). This classical procedure is justified because the 'in vivo' autoradiographic method is largely insensitive to small deviation in k^*_i values (Sokoloff *et al.*, 1977; Phelps *et al.*, 1979; Rougemont *et al.*, 1984), and because the lumped constant should not change meaningfully in nonextreme physiological conditions and within normal ranges of stable plasma glucose concentration (Schuier *et al.*, 1981), although the actual value is unknown in the baboon.

CMRGlc images. Following effective corpus callosum section, the initial (11 and 18 days after operation) PET images showed a diffuse reduction in CMRGlc in each animal

TABLE 1. PRE AND POSTOPERATIVE FLUORODEOXYGLUCOSE KINETIC RATE CONSTANT (k^*_{i1-3}) AND PLASMA GLUCOSE VALUES

	Control values			After callosotomy				
	Kiyosawa et al. *(n = 14)*	*Present series* *(n = 8)*		*Day 11* *(n = 3)*	*Day 18* *(n = 3)*	*Day 32* *(n = 3)*	*Day 56* *(n = 2)*	*Day 98* *(n = 2)*
k^*_1	0.086±0.007	0.074±0.003	(a)	0.079±0.005	0.076±0.001	0.069±0.004	0.068±0.005	0.076±0.009
			(o)	0.081±0.006	0.077±0.001	0.071±0.005	0.066±0.006	0.075±0.011
k^*_2	0.116±0.007	0.093±0.010	(a)	0.110±0.017	0.116±0.013	0.089±0.004	0.093±0.019	0.095±0.045
			(o)	0.113±0.015	0.109±0.013	0.086±0.009	0.085±0.018	0.089±0.042
k^*_3	0.0499±0.0025	0.043±0.003	(a)	0.040±0.005	0.041±0.003	0.041±0.002	0.048±0.004	0.044±0.006
			(o)	0.042±0.006	0.042±0.004	0.042±0.001	0.047±0.006	0.043±0.007
	(n = 7)	*(n = 4)*						
Glucose	5.06±0.44	5.33±0.72		4.83±0.22	4.89±0.17	5.00±0.44	4.61±0.11	4.83±0.22

Values shown are mean (±1 SEM) k^*_i values (min^{-1}) measured in the frontotemporal area (1 value per hemisphere) of 4 control Papio papio baboons (present study) and 7 control Papio anubis baboons (previous study, Kiyosawa *et al.*, 1989), and postoperatively in 3 corpus callosum-sectioned Papio papio baboons on the surgically approached (a) and opposite (o) sides (*see* Methods). The number of determinations is indicated in parenthesis. Corresponding plasma glucose values (mmol/l) are also shown. There were no significant differences either between the present and previous control k^*_i or plasma glucose values (t test), or among the time points in the present series (one-way ANOVA).

(fig. 2). This metabolic depression was particularly apparent in the frontal area of the surgically approached side, resulting in a mild but visible asymmetry (range 6−13%) in the OM +15 and +20 mm images; in the sham-operated animal, no obvious change in CMRGlc images was observed. These metabolic effects in the approached frontal area presumably represent the surgical area (artefact) and were therefore not analysed further.

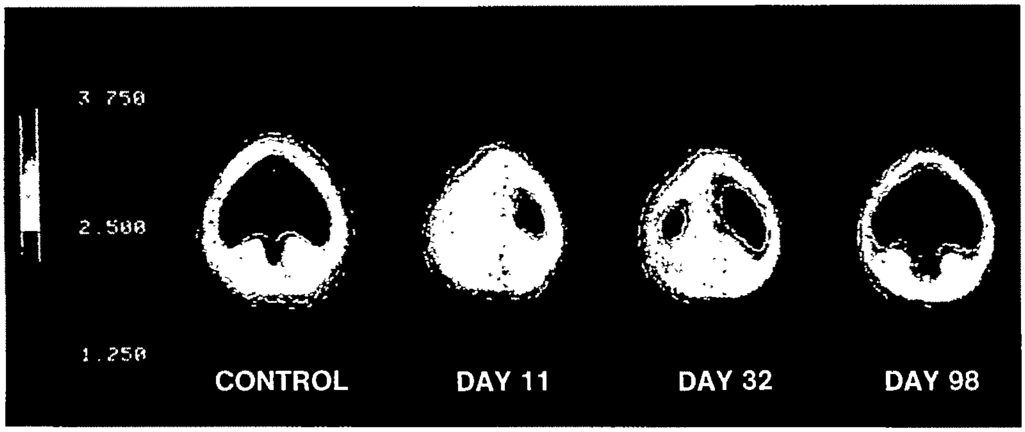

FIG. 2. Serial quantitative PET images of cerebral glucose utilization (CMRGlc) obtained at the OM +15 mm level before, and 11, 32, and 98 days after anterior corpus callosum section in baboon 2. The images are displayed using a pseudo-colour scale of absolute CMRGlc in mg/100 g · min. Bilateral but slightly asymmetric depression of CMRGlc with maximum effects in the anterior part of the brain is seen at day 11 with subsequent metabolic recovery.

CMRGlc data. To overcome the fact that 2 postoperative CMRGlc values were missing in baboon 3 (day 56 and day 98), we chose to abandon the ANOVA with repeated measures, and to use instead the ANOVA without repetition. To compensate the loss of statistical power, we sought to increase the number of control values to which the effects of corpus callosum section would be compared. To this end, the preoperative values (n = 4) of this series and those of 9 Papio anubis baboons from a previous experimental protocol (Kiyosawa *et al.*, 1989) were combined. This was possible as these two groups of CMRGlc control values were not significantly different from each other by the t test.

1. General findings. The preoperative and postoperative mean CMRGlc (±1 SEM) values are shown in Table 2. The ANOVA revealed significant effects of both the time factor ($P < 0.0001$) and the region factor ($P < 0.0001$), with no interaction between these two factors. Significant *time* effects were as follows: preop. > 11 days ($P < 0.01$), preop. > 18 days ($P < 0.01$), preop. > 32 days ($P < 0.01$), preop. > 56 days ($P < 0.01$), preop. > 98 days ($P < 0.05$), 18 days < 98 days ($P < 0.01$) and 32 days < 98 days ($P < 0.01$). Significant time effects by Newman-Keuls procedure for each region independently were present only in the frontotemporal and the temporal areas of the surgically approached hemisphere. However, if the data of the 'approached'

TABLE 2. REGIONAL CEREBRAL METABOLIC RATE OF GLUCOSE BEFORE AND AFTER CALLOSOTOMY[1]

		Preop. *(n = 13)*	*Day 11* *(n = 3)*	*Day 18* *(n = 3)*	*Day 32* *(n = 3)*	*Day 56* *(n = 2)*	*Day 98* *(n = 2)*
Frontotemporal area	(a)	5.41±0.22	4.03±0.43	3.80*±0.30	4.34±0.23	4.58±0.64	5.05±0.70
	(o)	5.39±0.23	4.34±0.29	4.13 ±0.35	4.75±0.37	4.74±0.42	5.26±0.56
Temporal area	(a)	4.93±0.25	3.70±0.31	3.48*±0.16	3.98±0.25	4.17±0.31	4.52±0.57
	(o)	4.92±0.26	3.87±0.23	3.70 ±0.17	4.22±0.29	4.32±0.23	4.66±0.49
Occipital area	(a)	4.15±0.16	3.38±0.25	3.42 ±0.07	3.52±0.17	3.45±0.35	3.42±0.06
	(o)	4.16±0.17	3.59±0.26	3.49 ±0.08	3.72±0.27	3.51±0.39	3.49±0.17

[1] Values are shown as mean ± 1 SEM (mg/100 g·min) on the numbers in parenthesis. (a) = surgically approached side, (o) = opposite site. * Significantly different from control values ($P < 0.05$) based on the Newman-Keuls test (*see* Results section for detailed findings using ANOVA).

hemisphere are omitted, the ANOVA performed on the opposite, 'intact' hemisphere also showed significant *time* effects as follows; preop. > 11 days ($P < 0.01$), preop. > 18 days ($P < 0.01$) and 18 days < 98 days ($P < 0.05$).

In order to confirm the results just described, various methods were designed to analyse the data using ANOVA with repeated measures, despite the 2 missing values. Hence, discarding the values for baboon 3 still allowed to observe in the remaining 2 animals significant time and region effects ($P < 0.001$ and < 0.00005, respectively). Discarding the day 56 and day 98 values of all 3 baboons resulted in equally significant findings, and revealed a statistically significant initial fall of CMRGlc and subsequent recovery. Estimating the 2 missing values either by time interpolation between the day 32 and day 207 values of baboon 3, or by the general method (Winer, 1971) led to essentially

TABLE 3. CEREBRAL METABOLIC RATE OF GLUCOSE IN THE FRONTOTEMPORAL AREA IN THE 3 CALLOSOTOMIZED BABOONS AND THE SINGLE SHAM-OPERATED BABOON[1]

Baboon		*Preop.*	*Day 11*	*Day 18*	*Day 32*	*Day 56*	*Day 98*
1	(a)	5.22	4.82 (−8%)	3.28 (−37%)	4.44 (−15%)	5.22 (0%)	5.74 (+10%)
	(o)	5.23	4.90 (−6%)	3.48 (−34%)	4.57 (−13%)	5.16 (−1%)	5.82 (+11%)
2	(a)	4.68	3.34 (−29%)	3.80 (−19%)	3.72 (−20%)	3.94 (−16%)	4.35 (−7%)
	(o)	4.72	3.95 (−16%)	4.27 (−9%)	4.21 (−11%)	4.32 (−8%)	4.70 (0%)
3	(a)	5.73	3.92 (−32%)	4.32 (−25%)	4.86 (−15%)	NA	4.99* (−13%)
	(o)	5.86	4.16 (−29%)	4.65 (−21%)	5.45 (−7%)	NA	5.15* (−12%)
Sham-operated	(a)	4.64	4.65 (0%)	4.74 (+2%)	5.13 (+11%)	NA	4.41 (−5%)
	(o)	4.52	4.88 (+8%)	4.74 (+5%)	5.13 (+13%)	NA	4.52 (0%)

[1] Values shown are in mg/100 g·min with percentage changes relative to corresponding preoperative value. (a) = surgically approached side, (o) = opposite side. * Values shown are from the day 207 study (*see* Results). NA = not available.

similar findings, namely (1) significant time and region effects ($P < 0.00001$); (2) significant initial depression of CMRGlc ($P < 0.01$) and subsequent recovery ($P < 0.05$ to 0.01 depending on the time); and (3) significant metabolic effects of lesion in both the surgically approached ($P < 0.01$ to 0.05) and the opposite frontotemporal region ($P < 0.05$).

2. Time-course of effects. Table 3 shows the individual preoperative and postoperative CMRGlc values in the frontotemporal areas in each of the four animals. The individual postoperative time course of frontotemporal CMRGlc relative to the corresponding preoperative values measured in the same animal is also illustrated in fig. 3. After callosotomy, a maximal CMRGlc decrease was found at 11 days in 2 of 3 animals (32% and 29%, respectively), and at 18 days in the third (37%). Recovery of CMRGlc was already complete in baboon 1 at 56 days, but not quite complete in baboon 2 at 98 days. In baboon 3, the data obtained 207 days after surgery showed a partial metabolic recovery (reduction of 13% and 12%, relative to preoperative values in the approached and the opposite frontotemporal area, Table 3).

Estimation of recovery was performed on the postoperative mean regional CMRGlc values using a nonlinear least square fitting method to the following monoexponential model (Kiyosawa *et al.*, 1989), using each animal's preoperative values as the asymptotic, full recovery, value:

$$\mathrm{CMRGlc} = a_1 - a_2 \cdot e^{-\ln 2 \cdot t/T}$$

where

a_1 is the asymptotic (full recovery) CMRGlc value (mg/100 g·min),
a_2 is the maximal CMRGlc decrease (mg/100 g·min), and
T is the half recovery time (days).

With this method, the frontotemporal and temporal region data, but not the occipital cortex data, could be fitted to the above model. The maximal CMRGlc decreases found were strikingly similar among these different regions (range 1.4–1.8 mg/100 g·min); the half recovery times were around 2 months and were also roughly constant (Table 4).

3. Regional effects. The significant *regional* effects of corpus callosotomy revealed by the global analysis of variance (*see* above) were also evaluated by the Wholly Significant Differences procedure with *Q*-values for pairs of regions: this procedure showed no significant difference for the 3 homologous pairs, but significant differences ($P < 0.05$) for each of the 3 pairs of regions within each hemisphere. These regional effects were also evaluated by the study of the intrahemispheric anteroposterior metabolic gradient, using the frontotemporal/occipital CMRGlc ratio (Table 5). The ANOVA performed on these data showed that the anteroposterior gradient was significantly depressed at days 11, 18 and 32 ($P < 0.01$) and was actually exaggerated, relative

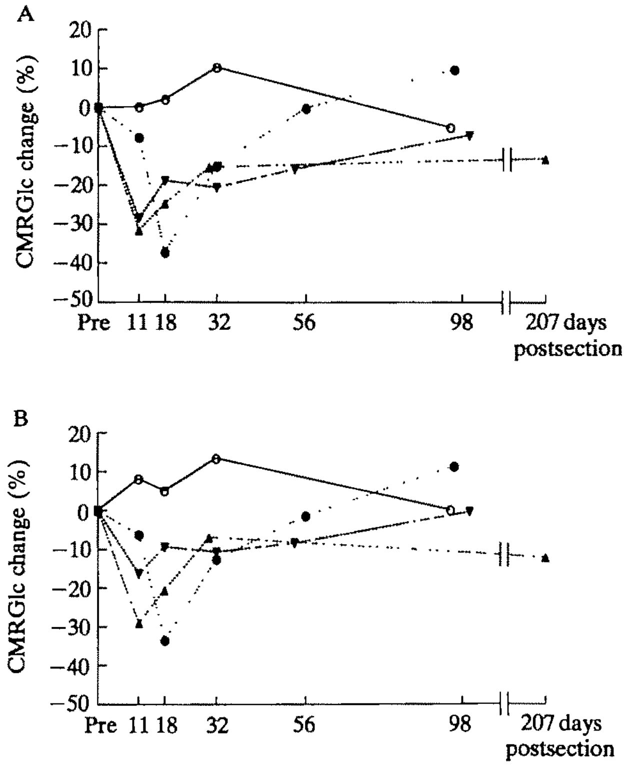

FIG. 3. The sequence of percentage change in cerebral glucose utilization (CMRGlc) in the surgically-approached (A) and opposite frontotemporal (B) area (OM +15 mm), determined in each of the 4 animals (corpus callosum section 1 (●), 2 (▼) and 3 (▲), and 'sham' (○) animal), relative to the corresponding preoperative values.

TABLE 4. ESTIMATED MAXIMAL CMRGlc DECREASE AND HALF RECOVERY TIME IN VARIOUS REGIONS OF INTEREST AFTER CALLOSOTOMY

Region of Interest		*Estimated maximum CMRGlc decrease (mg/100 g·min)*	*Half recovery time (days)*
Frontotemporal area	(a)	−1.8	67
	(o)	−1.4	54
Temporal area	(a)	−1.6	75
	(o)	−1.4	61

See Results section for description of the monoexponential model.
(a) = surgically approached side; (o) = opposite side. The occipital data could not be fitted.

to preoperative value, at 98 days ($P < 0.01$). These effects were more apparent in the approached side (fig. 4).

Sham-operated animal. Compared with the preoperative values, there was no apparent metabolic reduction following surgery (Table 3, fig. 3); the anteroposterior metabolic gradient was strikingly stable over time (fig. 4).

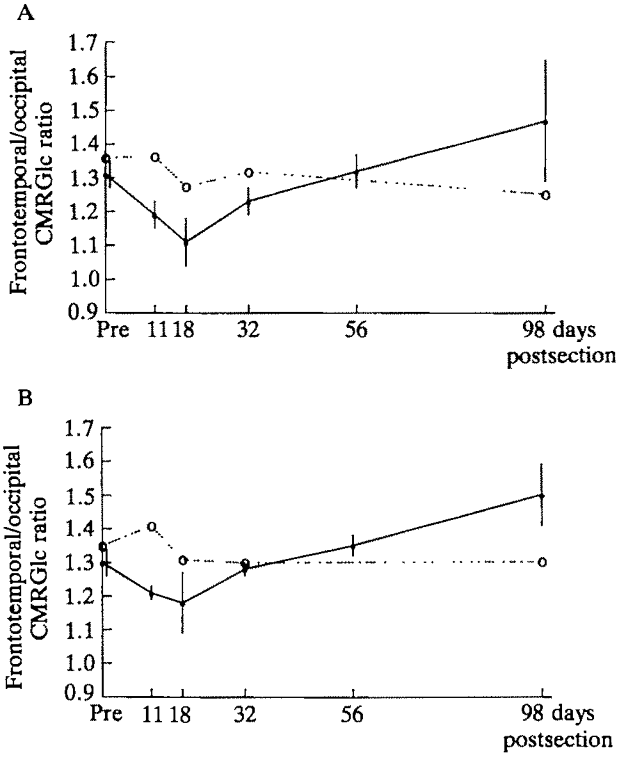

FIG. 4. Time-course of the frontotemporal/occipital CMRGlc ratio in corpus callosum sectioned baboons (n = 3, mean ± SEM) and in the sham-operated animal. A, approached side; B, opposite side. Closed circles = callosotomy; open circles = sham operation.

TABLE 5. RATIO OF CMRGlc BETWEEN THE FRONTOTEMPORAL AND THE OCCIPITAL AREAS BEFORE AND AFTER CALLOSOTOMY[1]

	Preop. *(n = 13)*	*Day 11* *(n = 3)*	*Day 18* *(n = 3)*	*Day 32* *(n = 3)*	*Day 56* *(n = 2)*	*Day 98* *(n = 2)*
Approached side	1.31±0.04	1.19±0.04	1.11±0.07	1.23±0.04	1.32±0.05	1.47±0.18
Opposite side	1.30±0.04	1.21±0.02	1.18±0.09	1.28±0.02	1.35±0.03	1.50±0.09

[1] Values are shown as mean ± 1 SEM (numbers of determinations in parenthesis). Statistically significant effects of surgery were demonstrated by ANOVA on these data (*see* Results).

DISCUSSION

The results of the present study indicated that effective anterior two-thirds corpus callosum section in 3 young adult baboons initially induced a significant reduction in cortical glucose utilization (range 6–37%, 11–18 days postsurgery) that predominated in the anterior parts of the brain and over the surgically approached side, and was followed by a slow but significant recovery, not consistently complete by 98 days; sham operation, by contrast, had no detectable effect on CMRGlc.

This is the first study that describes serial metabolic effects of corpus callosum section in primates. The stereotaxic approach, chosen both for its limited invasiveness and its technical ease, consistently resulted in effective anterior callosal section without complications. However, a circumscribed area of contusion in the medial aspect of the 'approached' frontal lobe could not be avoided. Although smaller than in the 3 callosotomized animals, this unwanted damage was also present in the sham-operated baboon, in which the metabolic changes were negligible. Hence this complication was presumably not entirely responsible for the changes seen in the effectively sectioned animals. Two further nonspecific effects of surgery could play a part in the metabolic changes observed. First, the low spatial resolution of the PET device could have smeared over the whole brain the metabolic changes that inevitably occurred within and around the surgical wound. Although this area was visible at a slight asymmetry in anterior frontal CMRGlc (*see* Results), both the statistical analysis and the monoexponential fitting procedure disclosed significant metabolic effects in the *contralateral* frontotemporal and temporal regions. Based on phantom studies, these distant effects cannot be due to the partial volume effect (Kiyosawa *et al.*, 1989). The other potential artefact entails a nonspecific 'neurosurgery effect' (e.g., subarachnoid bleeding) which, although unlikely, is nevertheless difficult to exclude as our sham animal was inevitably subjected to less invasive surgery. On the whole, therefore, it can reasonably be assumed that most of the metabolic effects observed in our animals did result from interhemispheric disconnection.

There are no comparable data in the literature on metabolic changes following callosal disconnection. One ^{14}C-2-deoxyglucose study in rats reported (in abstract form) semiquantitative data only (Soncrant *et al.*, 1986). Our findings are consistent with the fact that callosal afferents to the cortex are mainly excitatory (Innocenti, 1986); hence, interruption of callosal impulses would reduce synaptic activity and, in turn, CMRGlc, in the disconnected cortex. Similar bilateral metabolic effects of cortical deafferentation in the human, the monkey or the rat brain have been documented following strictly unilateral lesions of the thalamus (Girault *et al.*, 1985; Baron *et al.*, 1986) or of the nucleus basalis of Meynert (London *et al.*, 1984; Orzi *et al.*, 1986; Kiyosawa *et al.*, 1987, 1989), and presumably underlie the behavioural impairment that follows such lesions (Feeney and Baron, 1986; Baron *et al.*, 1989). As was also the case after a unilateral Meynert nucleus lesion (Kiyosawa *et al.*, 1989), the cortical metabolic depression in the present study clearly predominated in the anterior part of the brain. In the former, this pattern of metabolic effects was consistent with the topography of the basal-cortical cholinergic projections (Kiyosawa *et al.*, 1987, 1989). Although there is no strict regional homology of the callosal fibres within the cerebral hemisphere (both anterior and posterior cortical areas being connected to each contralateral cortical area), there is overall a predominance of homologous over heterologous fibres (Innocenti, 1986). Hence, the preferentially anterior distribution of metabolic effects in our animals presumably reflects the fact that the callosotomy was partial and left intact the occipital callosal homologous fibres. Alternatively, it could express the regional arrangement of the callosal fibres, such that the primary sensory cortices, including the visual cortex, have fewer callosal connections than the 'association' cortices (Innocenti, 1986).

Despite the above-noted similarities in the metabolic effects of callosal section and Meynert lesions in baboons, there are two noteworthy differences. First, the magnitude of the maximal cortical metabolic depression averaged 30% in the former and 45% in the latter, indicating a lesser influence of the callosal, relative to the cholinergic, afferents on the cortex. Secondly, differences must exist in the mechanisms of cortical metabolic depression, as callosal section interrupts the axons while the Meynert lesion damages mainly the nerve cell bodies. Because glucose utilization reflects the integrated synaptic activity, anterograde degeneration of presynaptic terminals, retrograde degeneration of neuronal soma, or transynaptic functional depression may all result in similar, indistinguishable metabolic effects. As callosal neurons may account for a sizeable proportion of all cortical neurons (Innocenti, 1986), the metabolic effects seen here may partly result from actual nerve cell degeneration; however, retrograde somatic degeneration seems not to occur after callosal section in adult cats (Innocenti, 1986), so that the metabolic effects reported here are presumably only anterograde, either presynaptic (degeneration) or postsynaptic (loss of excitory impulses), or both.

Following the initial effects of corpus callosum section, a gradual recovery towards normal metabolic activity was demonstrated by the analysis of variance, the monoexponential fitting procedure, and the data analysis on the anteroposterior metabolic ratio; this recovery was complete in the first 2 animals and apparently partial in the third. A similar recovery of cortical metabolism has been reported after unilateral lesions of the thalamus in man (Baron *et al.*, 1986, 1989; Cambon *et al.*, 1987) or of the nucleus basalis of Meynert in rats (London *et al.*, 1984; Orzi *et al.*, 1986) and baboons (Kiyosawa *et al.*, 1987, 1989), and now appears as a consistent feature of the deafferented cerebral cortex. Possible mechanisms for this recovery have been extensively discussed in the case of the Meynert lesion (Kiyosawa *et al.*, 1989). Following corpus callosum section, either reinnervation (sprouting) by collaterals of nonsevered callosal neurons, or reorganization of the neuronal circuitry, or a process of postsynaptic hypersensitivity, may all provide effective compensation for, and slowly restore synaptic activity within, the deafferented cortex, although we are not aware of any relevant ultrastructural study. Most of this remarkable adaptive process is presumably mediated by the posterior one-third of the corpus callosum, through connections between the posterior cerebral cortices and the entire contralateral cortical ribbon. In the rat, however, hypertrophic changes of cholinergic neuron somas in the basal nucleus have been observed following callosal section (Pearson *et al.*, 1985, 1987), indicating that neuronal adaptation to this lesion may also involve noncortical neuronal systems. The exaggerated anteroposterior metabolic gradient seen here 98 days after anterior callosal section may reflect altered functional organization of cortical circuits as a result of such mechanisms.

In the clinical setting, partial anterior corpus callosum section aimed at improving medically intractable epilepsy initially induces in most cases a transient behavioural impairment, in the form of speech disturbances with near mutism, an acute disconnection syndrome, and/or a transient deficit in motor coordination (Sussman *et al.*, 1983; Purves *et al.*, 1988; Spencer, 1988). This impairment tends to recover over days to months and a persistent neurological deficit does not necessarily ensue (Gordon *et al.*, 1971;

Wada, 1987; Purves *et al.*, 1988; Spencer, 1988). Our data showing initial major effects on, and subsequent recovery of, cortical, predominantly frontotemporal, metabolic activity after anterior partial corpus callosum section would be consistent with, and would provide a mechanism for, these clinical observations.

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THE ORIGIN OF REMYELINATING OLIGODENDROCYTES IN ANTISERUM-MEDIATED DEMYELINATIVE OPTIC NEUROPATHY

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SUMMARY

The origin of the remyelinating oligodendrocyte in a focal antigalactocerebroside-induced demyelinating lesion of the cat optic nerve was studied with detailed correlative electron microscopy and immunocytochemistry using a panel of antigenic markers. Within 10 days of the destruction of all endogenous oligodendrocytes and demyelination of all axons in the lesion, a new population of small glial cells appeared coincident with division of the residual astrocytes and developed a process-bearing axon-embracing morphology. The processes of these small glial cells (SGCs) contained intermediate filaments composed not of glial fibrillary acidic protein but of vimentin and over the ensuing 14 days these cells confirmed their oligodendrocyte destiny by differentiating to lose the intermediate filaments, form myelin and acquire the typical oligodendrocyte antigenic phenotype. It is suggested that the extensive remyelination of this lesion is sponsored by the new population of SGCs which in turn are generated either by dedifferentiated reactive astrocytes or by as yet unidentified precursor cells.

INTRODUCTION

Twenty years ago remyelination in the central nervous system (CNS) was considered at best to be limited (Bunge, 1968). Since then it has been demonstrated conclusively that such is not always the case and that the restoration of secure conduction of trains of impulses after CNS demyelination depends on remyelination (McDonald and Sears, 1970; Smith *et al.*, 1981; Carroll *et al.*, 1985*b*). Despite the study of an increased number and variety of experimental models of demyelination, the origin of the remyelinating oligodendrocyte remains unclear. One important and relevant aspect in this regard is the variable extent of remyelination in both human demyelinating diseases, such as multiple sclerosis (Prineas and Connell, 1979; Ghatak *et al.*, 1988), and experimental demyelination (Blakemore, 1982).

In some experimental models of demyelination in which the oligodendrocytes and myelin are selectively destroyed but the astrocytes are spared, such as with cuprizone (Blakemore, 1972; Ludwin, 1978), or antibody-mediated injury (Saida *et al.*, 1979; Carroll *et al.*, 1984, 1985*a*), remyelination is nearly complete. In contrast, with less selective gliotoxic demyelinating agents such as lysolethicin (Blakemore, 1978), 6-aminonicotinamide (Blakemore, 1975) and diphtheria toxin (Eames *et al.*, 1977;

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Murray and Noble, 1985), remyelination is more restricted and slower. Such observations do not necessarily imply that the limited remyelination in multiple sclerosis (Prineas and Connell, 1979) occurs simply because of a nonselective glial insult, but they do give an indication that both astrocytes and/or glial precursors might be required for successful remyelination. Indeed, early work by Bunge *et al.* (1960, 1961), using a CNS barbotage model of demyelination studied ultrastructurally, suggested that the remyelinating oligodendrocyte might be derived from astrocytes, and the close association between astrocytes and oligodendrocytes has been a long running controversy (Ramón-Moliner, 1958; Smart and Leblond, 1961; Pessacq, 1964; Polak, 1965; Wisniewski *et al.*, 1977; Munoz-Garcia and Ludwin, 1985). The development of cell-type specific antigen immunocytochemistry to characterize glial cells (Eng *et al.*, 1971; Raff *et al.*, 1978; Eisenbarth *et al.*, 1979) has provided an independent parameter for the identification of morphologically similar or immature cell lines. This has rekindled interest in the histogenesis of the principal glial cells, especially the oligodendrocyte, and facilitated the study of glial cells in CNS demyelination and remyelination.

In the developing human (Choi *et al.*, 1983) and mouse (Choi, 1986) spinal cord it has been argued that oligodendrocytes arise from astroglial precursors, and that they briefly coexpress astrocyte-specific glial fibrillary acidic protein (GFAP). Raff *et al.* (1983) identified a bipotential progenitor cell from cultures of developing rat optic nerve which could develop along one or other glial lineage. This bipotential cell was subsequently termed the oligodendrocyte type 2 astrocyte (O-2A) progenitor cell (Raff *et al.*, 1984), and it has also been found in small numbers in the adult rat optic nerve (ffrench-Constant and Raff, 1986*a*). Importantly, by manipulation of the culture conditions, these bipotential cells from rat optic nerve (Temple and Raff, 1985) and adult human corpus callosum (Kim *et al.*, 1985) can express either astrocyte or oligodendrocyte antigens without cell division, indicating considerable plasticity of these cells.

We have studied a selective demyelinating lesion in the cat optic nerve in which all oligodendrocytes are destroyed (Carroll *et al.*, 1984, 1985*a*) but which is reliably followed by almost complete remyelination. An earlier preliminary immunocytochemical study of this lesion addressed the origin of the remyelinating oligodendrocyte by using antibodies to galactocerebroside (GC) and GFAP. On the basis of dual staining of glial processes with these antibodies it was suggested that remyelinating oligodendrocytes were generated from dedifferentiated residual astrocytes (Carroll *et al.*, 1987).

In the present report we describe the results of a detailed correlative ultrastructural and light microscopic immunocytochemical study using serial sections, an expanded panel of antigenic markers, a larger number of lesions and an extended period of observation which has enabled individual glial cells to be fully characterized and glial cell populations to be quantitated. Important observations have been made in three areas: (1) the origin of the remyelinating oligodendrocyte, (2) the ultrastructural and immunocytochemical features of the oligodendrocyte precursor, and (3) the relationship between events in this model of demyelination and those of myelinogenesis and remyelination in general.

METHODS

Optic nerve lesion and preparation

Under Saffan (Glaxo) constant infusion anaesthesia and assisted ventilation, the right intraorbital optic nerve of 21 young adult cats (2.0 – 3.0 kg) was exposed. In 16 cats 1 – 3 μl of high titre anti-GC antiserum was slowly injected through a 40 μm micropipette (Carroll *et al.*, 1985*a*). At intervals after injection of 2 days (1 cat), 3 days (2 cats), 4 days (1 cat), 5 days (1 cat), 6, 7, 9 and 12 days (2 cats each) and 14, 17 and 24 days (each 1 cat) the animals were deeply anaesthetized and perfused with 1.25% glutaraldehyde and 3% paraformaldehyde in phosphate buffer (pH 7.4). The right and left (control) optic nerves were removed, postfixed in 2% osmic acid, processed routinely (Sakura REM 200B) and embedded in Araldite. 1 μm sections were cut and stained with toluidine blue to select the best block for detailed analysis using light microscopic immunocytochemistry and electron microscopy (EM). The remaining 5 animals had similar quantities of nonimmune serum injected and were examined in the same fashion after intervals of 7 days (2 cats), and 8, 13 and 18 days (1 cat each) postinjection.

Ultrastructure and immunocytochemistry

Five consecutive 1 μm sections were cut (LKB Ultracut ultramicrotome) and mounted individually on glass slides, after which adjacent thin sections (70 – 80 nm) were cut and collected on carbon and formvar-coated slot aperture grids and stained with uranyl acetate and lead citrate. The first of the five 1 μm sections was stained with toluidine blue, and the remaining 4 were deplasticized (Winchell *et al.*, 1982) before being immunostained using the peroxidase-antiperoxidase method (Sternberger *et al.*, 1970). Overnight exposure to the primary antisera (anti-GFAP, antivimentin (Vim), antigalactocerebroside (GC) and antimyelin basic protein (MBP)) at 4° C followed blocking with 20% normal swine sera. All antisera were diluted in tris buffered saline (TBS) containing 1% bovine serum albumin as follows: rabbit anti-GFA (Dako) at 1:100; mouse anti-Vim (Dako) at 1:60; rabbit anti-GC (Carroll *et al.*, 1987) at 1:80, and rabbit anti-MBP (Dako) at 1:50. Nonimmune rabbit serum at 1:40 was applied to one section in every run as a staining control. After washing in TBS, the sections were reacted for 30 min either in antirabbit peroxidase-antiperoxidase (PAP) complex or antimouse PAP, and after further washes were exposed to freshly prepared diaminobenzidine. A light haematoxylin counterstain was applied before mounting. Fig. 1 schematically represents the steps followed in this method.

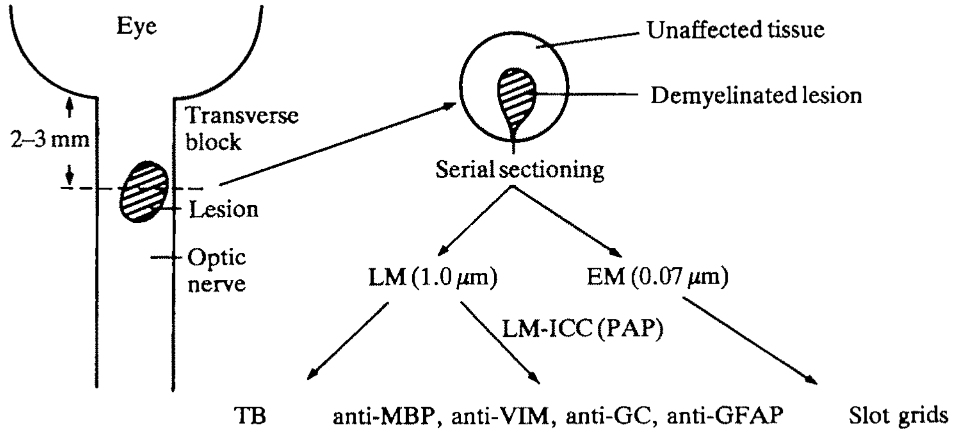


FIG. 1. Schematic representation of the experimental procedure. For each animal a block of optic nerve containing the lesion was sectioned serially to provide a set of 1.0 μm thick and 0.07 μm thin transverse sections which were then prepared for light microscopy (LM), light microscope-level immunocytochemistry (LM-ICC) and electron microscopy (EM) as described in the text. PAP = peroxidase-antiperoxidase technique; TB = toluidine blue; anti-MBP = antimyelin basic protein; anti-Vim = antivimentin; anti-GFAP = antiglial fibrillary acidic protein; anti-GC = antigalactocerebroside.

Quantitative analysis

LM photography was carried out on a Zeiss Universal Microscope using Ilford Pan F 35 mm film (ASA 50) printed at 20×25 cm (mag. ~ ×2000). A low power (×10 or ×25 OBJ) toluidine blue-stained overview of the whole lesion was followed by 5 typical high power fields (×100, oil immersion) from within the lesion which were then marked out on the low power photomicrograph.

Matching fields from the consecutive immunostained (anti-GFA, anti-Vim, anti-GC and anti-MBP) sections were then photographed and all prints were overlaid with detachable plastic sheets. Positive and negative immunostaining of cell bodies and processes was colour-coded directly onto each plastic overlay as each high power field was examined. For each antigen the positive cell counts from the 5 fields were summed and averaged, and differential staining patterns of individual cells were determined by overlaying the colour-coded plastic sheets and recording their immune staining profile on the toluidine blue print overlay (e.g., $Vim^-/GFA^-/GC^+$). Note that anti-MBP did not stain any cell bodies under our fixation and processing conditions, and likewise monoclonal anti-A2B5 antibody (Eisenbarth *et al.*, 1979) did not stain any cells in lesioned and normal optic nerve either in deplasticized or frozen sections, a finding attributed to species differences (ffrench-Constant *et al.*, 1988).

For ultrastructural description and photography of individual cells of interest, a Philips 201 EM was used to examine the adjacent slot grid which was orientated by reference to the overview print.

Autoradiography

Autoradiography was performed on 2 animals with 4 and 6 day lesions using tritiated thymidine (6-^3H Thy; Amersham International; specific activity 5.0 Ci/mmol) as a pulse dose of 1 mCi/kg administered i.v. 90 min before perfusion. 1 μm sections were coated with Ilford L4 emulsion and allowed to expose for 6 wks at 4° C before developing in D-19.

RESULTS

Control animals

In normal nonlesioned left optic nerves, and in the 5 control cats injected with nonimmune serum, tightly packed myelinated axons were separated into fascicles by connective tissue septa containing blood vessels. In control animals LM of toluidine blue-stained sections revealed a narrow needle track injury characterized by a number of fibres undergoing Wallerian-type degeneration. Glial cells were easily distinguished as astrocytes or oligodendrocytes ultrastructurally and immunocytochemically.

At the ultrastructural level astrocytes had uniform pale nuclei (~7.0 μm×3.5 μm) and copious electronlucent cytoplasm containing intermediate filaments. Oligodendrocytes had no intermediate filaments but plentiful microtubules, and ranged in morphology from medium density cells with large nuclei (up to 9.0×6.0 μm) to small dark cells with smaller rounded (~4.0 μm diameter) nuclei with clumped chromatin. Immunocytochemically the staining of oligodendrocytes and astrocytes was mutually exclusive (fig. 2 and Carroll *et al.*, 1987). $GFAP^+$ staining was seen in astrocyte cell bodies and in their long processes, the latter forming an interlacing 'matrix' of short profiles in the interaxonal spaces, as well as the glia limitans. Glial nuclei, oligodendrocyte cytoplasm and all other structures were $GFAP^-$. Compact myelin and oligodendrocyte cytoplasm were strongly GC^+, while weak background staining was evident in endothelial cells, astrocyte nuclei and axoplasm. MBP^+ staining was confined to compact myelin, while Vim^+ staining was restricted to some astrocyte processes. The

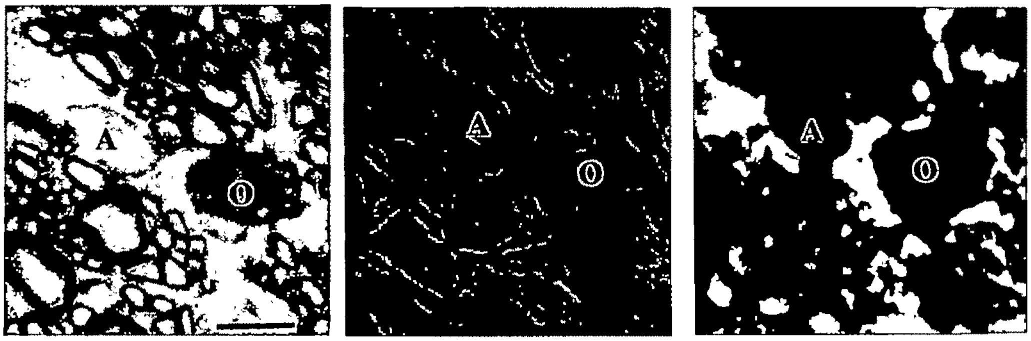


FIG. 2. Light photomicrographs of consecutive sections from a normal cat optic nerve. An astrocyte (A) lies adjacent to an oligodendrocyte (O) among myelinated axons in 3 consecutive 1 μm sections stained with toluidine blue (*left*), anti-GFAP (*middle*) and anti-GC (*right*). With anti-GFAP, brown reaction product stains the astrocyte cytoplasm as well as an extensive interaxonal 'matrix' of astrocyte processes but not the oligodendrocyte. With anti-GC, dense reaction product fills the oligodendrocyte cytoplasm and stains myelin sheaths but is absent from astrocyte cytoplasm. Note the nonspecific anti-GC staining of the astrocyte nucleus. Bar = 5 μm.

total glial cell count approximated 10 cells per high power field, with astrocytes (5.0 ± 0.8 per high power field) slightly outnumbering oligodendrocytes (4.8 ± 1.3 per high power field).

Lesioned animals

In each of the 16 anti-GC antiserum-injected optic nerves there was an area of demyelination which occupied 10–70% of the cross-sectional area of the nerve (fig. 3) and extended up to 2.5 mm along the nerve. The changes observed between 2 and 24 days postlesion are described in four main time periods: (1) demyelination, (2) glial proliferation, (3) premyelination and (4) remyelination.

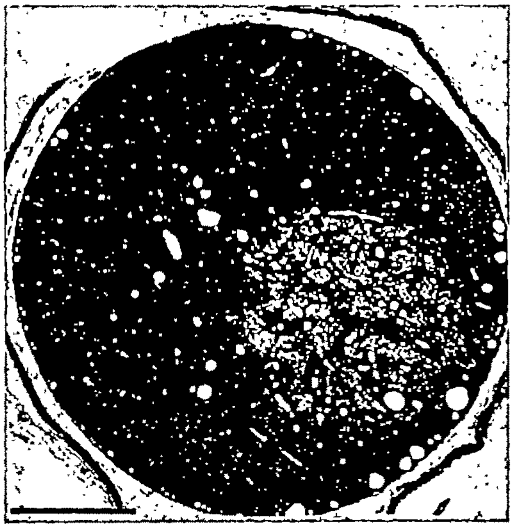


FIG. 3. Full-face transverse section of cat optic nerve. The focal area of demyelination is surrounded by unaffected fascicles of tightly packed myelinated fibres separated by connective tissue septa containing blood vessels. Bar = 500 μm.

Demyelination (2–3 days postinjection)

During this period the lesion was characterized by demyelination, the complete loss of oligodendrocytes, intense macrophage activity and astrocyte hypertrophy. The myelin sheaths of all axons within the lesion showed vesicular and degenerative change, but the axons remained normal. At 2 days, healthy oligodendrocytes were completely absent from the lesion, but some degenerating cells contained microtubules and retained GC^+ staining. By 3 days there were no GC^+ oligodendrocytes. The only glial cells were large $GFAP^+$ astrocytes. These large astrocytes had a reactive morphology comprising a uniform stellate appearance and an enlarged oval nucleus ($\sim 9.0\ \mu m \times 6.0\ \mu m$) with an even chromatin pattern often containing a single large nucleolus. Their copious medium density cytoplasm was relatively unorganized, containing many mitochondria, short single profiles of rough endoplasmic reticulum, free ribosomes and randomly orientated intermediate filaments but no myelin debris. While all the large reactive astrocytes had strongly $GFAP^+$ cytoplasmic processes, at 3 days some of these processes were also GC^+ and a few were Vim^+ (fig. 4). In keeping with the absence of myelin debris, none of these large reactive astrocytes was MBP^+. MBP^+ staining was confined to myelin debris in extracellular spaces and within the large number of macrophages, whose elaborate cytoplasmic processes were often in intimate contact with degenerating myelin sheaths and formed the major constituent of the interaxonal matrix during this period.

Glial proliferation (4–6 days postinjection)

This period was characterized by the complete clearance of extracellular myelin debris, striking astrocyte hypertrophy and hyperplasia, and the appearance of a new population of glial cells. By 4 days cleanly demyelinated axons were separated by myelin debris-laden macrophage cytoplasm and by straight glial cytoplasmic profiles rich in intermediate filaments, both of which reduced the amount of extracellular space. The reactive $GFAP^+$ astrocytes showed further nuclear enlargement, a general increase in cytoplasmic organelles and many of the cells had Vim^+ and GC^+ processes. The occasional mitotic figure in these cells (fig. 5) correlated with the autoradiographic finding

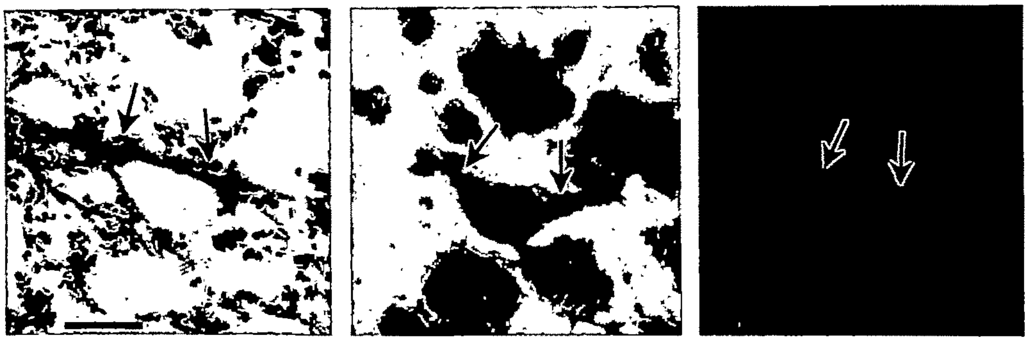


FIG. 4. Light photomicrographs of 3 consecutive sections from a typical 'demyelination period' field showing a strongly $GFAP^+$ (*left*), large reactive astrocyte with GC^+ (*middle*) and Vim^+ (*right*) processes (arrows). Bar = 5 μm.

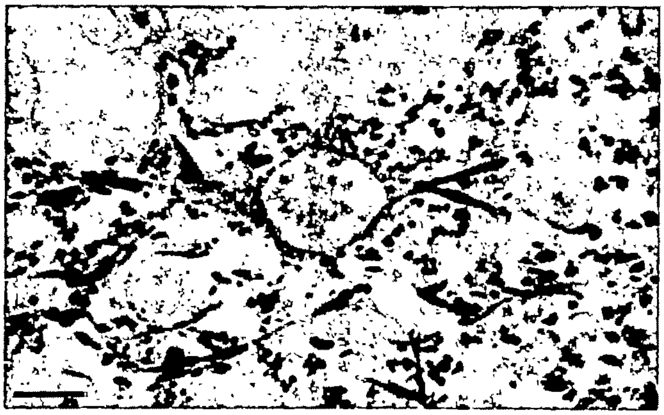


FIG. 5. Light photomicrograph of a mitotic astrocyte at 4 days postinjection with strong cytoplasmic immunostaining for GFAP. Bar = 5 μm.

at this time of frequent nuclear uptake of tritiated thymidine (up to 30%) indicating DNA synthesis in preparation for cell division. No dividing cells were seen outside the lesion but approximately 18% of endothelial cells within the lesion were labelled.

After a further 48 h (6 days postlesion), the total number of glial cells had almost doubled to approach the numbers seen in the normal optic nerve (fig. 6, Table), and now comprised two distinct populations of cells. The first consisted of the large reactive

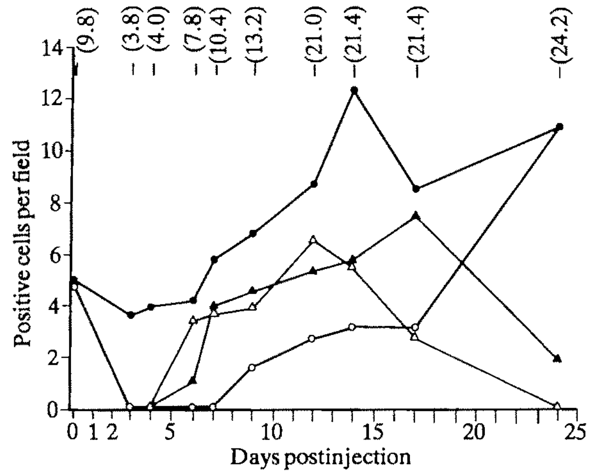


FIG. 6. Graph showing the number of glial cells (from the average of counts in 5 high power fields; *see also* Table) showing immunostaining for GFAP, GC and Vim over the 24 days after anti-GC microinjection. The figures in parentheses at the top of the graph indicate the total number of glial cells at each time point. GC_1 indicates small glial cells with GC positivity confined to their processes, whereas GC_2 indicates a normal oligodendrocyte pattern of GC^+ perinuclear cytoplasm. Note the dramatic fall in the number of GC^+ cells by 3 days followed by the appearance of Vim^+ and GC_1 cells which rise in parallel until 14–17 days and which is then followed by a steady decline in numbers of GC_1 and Vim^+ staining cells as the number of GC_2 cells increases. Filled circles = GFAP, open circles = GC_2, filled triangles = GC_1, open triangles = Vim.

TABLE. NUMBERS OF IMMUNOPOSITIVE GLIAL CELLS PER HIGH POWER FIELD ±SD*

	Days post injection									
Antigen	*0*	*3*	*4*	*6*	*7*	*9*	*12*	*14*	*17*	*24*
GFA	5.0	3.8	4.0	4.2	5.8	6.8	8.8	10.4	8.6	11.0
±	0.8	1.3	1.1	1.3	2.3	1.9	1.8	3.0	0.5	0.8
GC_2	4.8	0.0	0.0	0.0	0.0	1.6	2.8	3.2	3.2	11.0
±	1.3	0.0	0.0	0.0	0.0	1.5	1.3	1.8	1.1	2.5
GC_1	0.0	0.0	0.0	1.0	4.0	4.6	5.4	5.8	7.6	2.0
±	0.0	0.0	0.0	2.0	1.1	1.8	4.0	2.7	1.5	1.2
VIM	0.0	0.0	0.0	3.4	3.8	4.0	6.0	5.6	2.8	0.0
±	0.0	0.0	0.0	1.5	2.4	1.7	1.8	2.6	1.9	0.0
Total	9.8	3.8	4.0	7.8	10.4	13.2	21.0	21.4	21.4	24.2

* *See* fig. 6.

$GFAP^+$ cells which projected cytoplasmic processes containing bundles of intermediate filaments with or without microtubules, in both long straight profiles or more insinuating profiles among the demyelinated axons. The second and numerically minor population of glial cells had very small oval nuclei (up to 5.0×2.5 μm) with homogeneous medium dense chromatin (fig. 7A, B). The cytoplasm of these small glial cells (SGC) ranged from meagre and simple with a narrow perinuclear rim containing a few mitochondria,

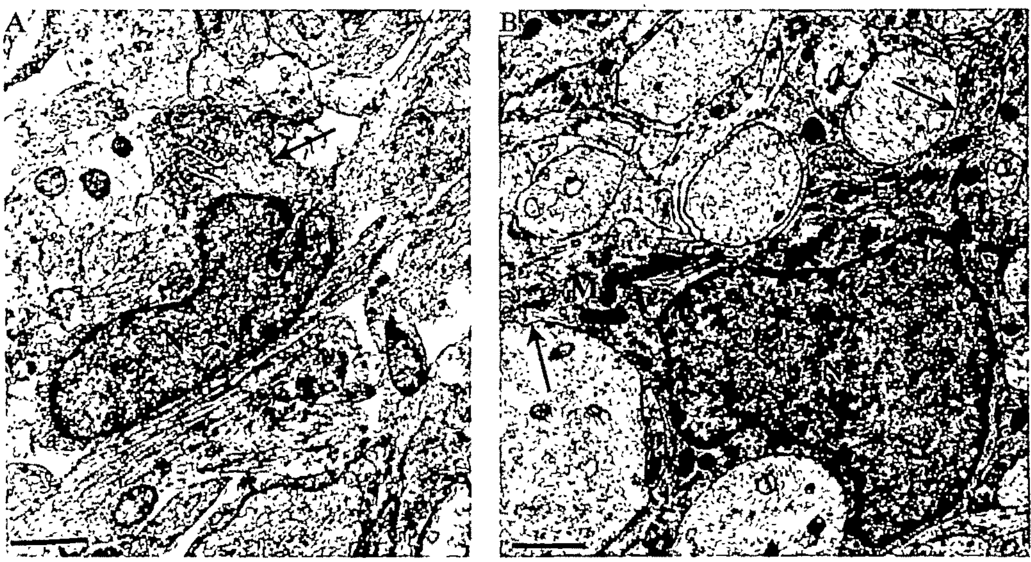


FIG. 7. Small glial cells at the time of earliest detection within the lesion (5–6 days postinjection). A, a nonprocess-bearing small glial cell with a small oval nucleus (N) and meagre amounts of perinuclear cytoplasm. A single outpocket of cytoplasm (arrow) can be seen to contain intermediate filaments. B, process-bearing small glial cell with more organelle-rich cytoplasm containing mitochondria (M), endoplasmic reticulum (ER) and intermediate filaments extending in slender axon-embracing processes (arrows). Bars = 1 μm.

short endoplasmic reticulum but many free ribosomes (fig. 7A) to a more organelle-rich and process-bearing morphology which included Golgi apparatus and both intermediate filaments and microtubules in their slender axon-embracing processes (fig. 7B).

There were also important and distinctive differences in immunostaining patterns between these two populations of glial cells. While the large astrocytes had strongly GFAP$^+$ cytoplasm and processes, the small glial cells were GFAP$^-$ but strongly Vim$^+$ in the perinuclear cytoplasm and processes. Quantitative assessment of GC staining in the latter at this stage was not attempted due to the large component of debris-laden GC$^+$ macrophage cytoplasm present in the matrix. MBP staining remained restricted to myelin debris within macrophages. Autoradiography performed at 6 days showed infrequent labelling of astrocytes (less than 5%) and endothelial cells (approx. 10%) but not of any small glial cells. Again, no cell division was detected outside the lesion.

Premyelination (7–12 days postinjection)

Over this 5 day period the interaxonal matrix became completely glial and began to show specialization and maturation culminating in the commencement of myelin formation by young oligodendrocytes. Numbers of both the astrocytes and particularly of the small glial cells increased to reach a total glial count of twice normal by 12 days (fig. 6, Table).

From 7 days most macrophages were confined to the perivascular regions, and glial processes occupied almost all of the interaxonal matrix. These processes were packed either with intermediate filaments only or admixed intermediate filaments and microtubules, the latter processes intimately embracing the demyelinated axons.

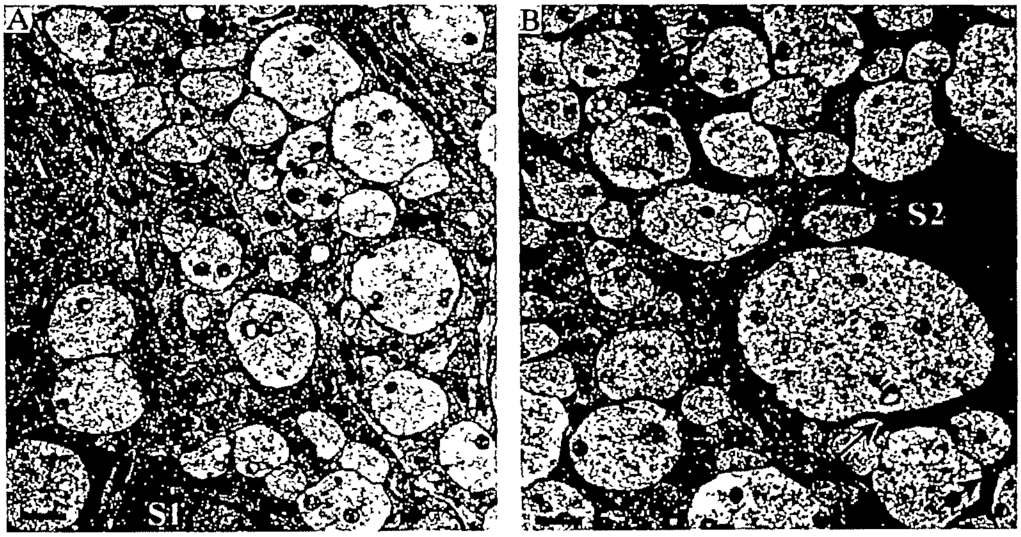
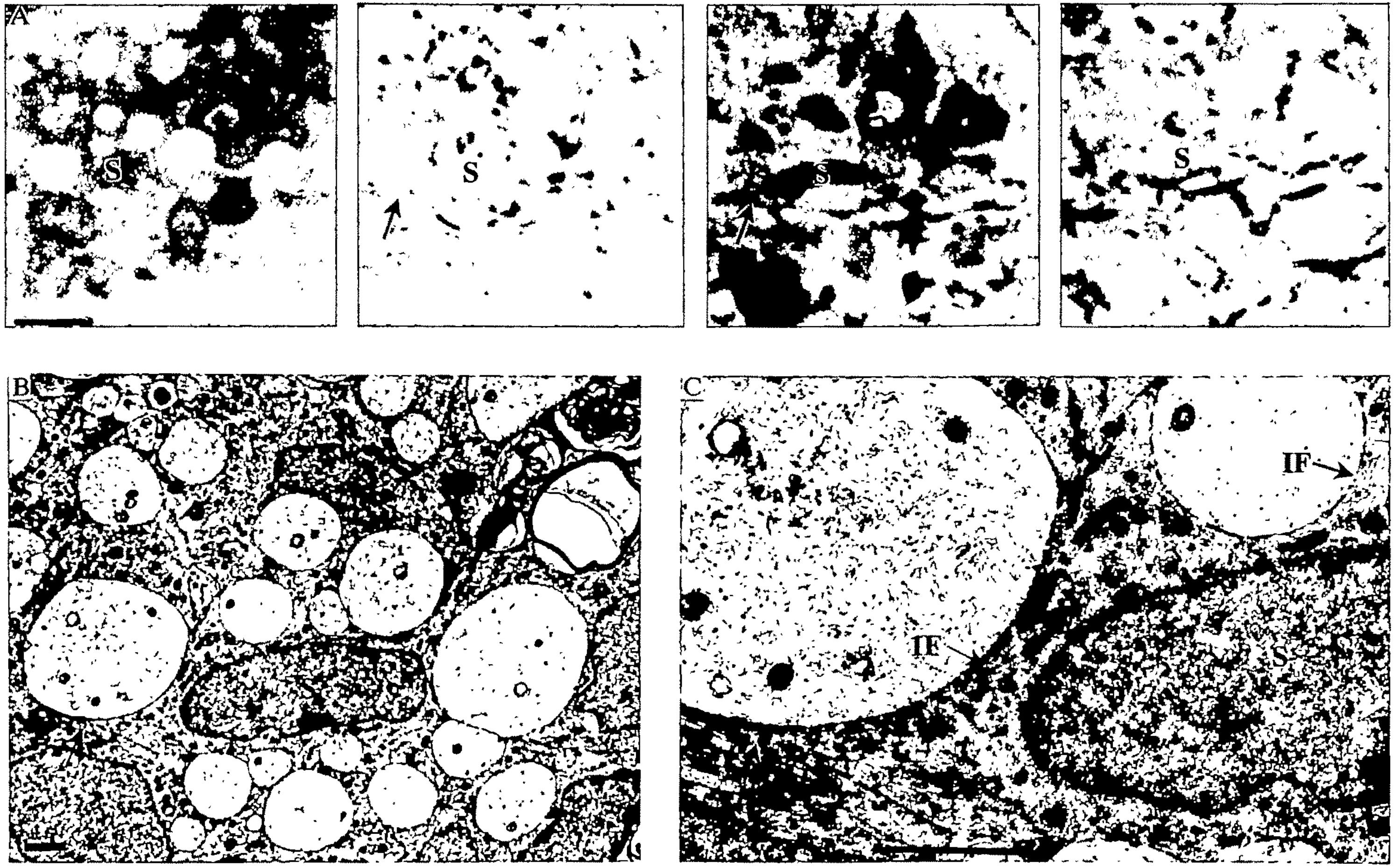


FIG. 8. Electron micrographs of early (A) and late (B) premyelinative lesion. A, the cytoplasmic processes arising from the astrocyte (A) and small glial cell (S1) are indistinguishable and contribute to the uniform matrix of processes, all of which contain intermediate filaments. B, a dark small glial cell (S2) has electron-dense processes and similar dark cytoplasmic profiles are present in the matrix (arrows). An occasional axon has a thin myelin sheath (star).


A
S
S
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S
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C
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IF
S

Both the large astrocytes and the small glial cells had an active organelle-rich medium density cytoplasm containing intermediate filaments. There were no glial cells or glial cell processes which did not contain intermediate filaments, so that individual processes were often indistinguishable unless continuous with their respective perikarya (fig. 8).

The antigenic characteristics of the large reactive astrocytes remained unchanged from 6 days but the increased numbers of SGCs, in addition to strong Vim$^+$ staining, also had GC$^+$ processes. Fig. 9 is of a typical premyelination field and illustrates the combination of immunocytochemistry and EM used in the identification and characterization of these SGCs showing their Vim$^+$/GFAP$^-$/GC$^+$ processes in intimate contact with nearby bare axons. This pattern of GC$^+$ staining confined to SGC processes was designated GC$_1$ to distinguish it from the strong perinuclear pattern characteristic of normal oligodendrocytes (fig. 2) and which was designated GC$_2$. The interaxonal matrix now comprised GFA$^+$, Vim$^+$ and GC$^+$ intimate periaxonal rings and straighter profiles, which ultrastructurally were of medium or low electron density.

From 9 days onwards, denser darker cytoplasmic profiles in close contact with axons became increasingly evident in the matrix (fig. 8B), and by 12 days many axons were surrounded by them and an occasional axon had up to 3 myelin lamellae. In parallel with these changes in the composition of the glial matrix, some SGCs now had darker nuclei with clumped chromatin and more electron-dense perinuclear cytoplasm which extended in multiple axon-wrapping processes. By LM and even low power EM these dark SGCs appeared to form a single population (fig. 10). However, correlative high power EM and ICC revealed that in fact two groups of cells were present (fig. 10B, C). The first cell type still featured cytoplasm rich in intermediate filaments, which was strongly Vim$^+$ and process-only GC$^+$, characteristic of the paler GC$_1$ SGCs (i.e., Vim$^+$/GFA$^-$/GC$^+$; fig. 10B). The less commonly encountered second type of dark SGC, however, had microtubules but no intermediate filaments, was Vim$^-$ and had strongly GC$^+$ perinuclear cytoplasm (i.e., GC$_2$ or Vim$^-$/GFA$^-$/GC$^+$; figs 10C, 11). Thus both morphologically and immunocytochemically, these latter cells conformed to the criteria for oligodendrocytes. Furthermore, only these GC$_2$ cells were associated with compact myelin lamellae or the corresponding MBP$^+$ periaxonal rings seen with LM.

Remyelination (14–24 days postinjection)

By 24 days almost all axons had several lamellae of compact myelin, the remyelinating cells were clearly indentifiable as oligodendrocytes and total glial cell numbers remained

FIG. 9 (opposite page). Detail of a typical premyelination field as revealed by correlative light microscope level—immunocytochemistry and EM. A, photomicrographs of 4 consecutive 1 μm sections stained with (from *left* to *right*) toluidine blue, anti-Vim, anti-GC and anti-GFAP. A small glial cell (SGC;(S)) lies horizontally across the middle of the field among cleanly demyelinated axons and with other SGCs surrounding it. Note that the toluidine blue-stained section does not pass through the nucleus of cell S, but the surrounding axons delineate its cytoplasm. This SGC (S) is positive for Vim, process-only positive for GC (arrow) but negative for GFAP (i.e., Vim$^+$/GFA$^-$/GC$^+$, an immunostaining pattern termed GC$_1$ - *see* text for details). Bar = 5 μm. Low power (B) and higher power (C) electron micrographs of the same SGC (S) as in fig. A from the adjacent slot grid show the ultrastructure and morphology typical of these cells, i.e., a small regular nucleus with limited but organelle-rich medium density perinuclear cytoplasm extending as slender processes around nearby axons. Note the intermediate filaments in C, which are a feature of these cells and the process emanating from the cell body which, as shown in A (arrow), is both Vim$^+$ and GC$^+$. Bars = 1 μm.

elevated (fig. 6, Table). Remyelination proceeded uniformly throughout the lesion with no emphasis or enhancement at the lesion edge. The percentage of axons with myelin increased from 1% at 14 days to 95% by 24 days, and over this period there was a steady increase in the number of myelin lamellae (fig. 12). By 24 days there were some

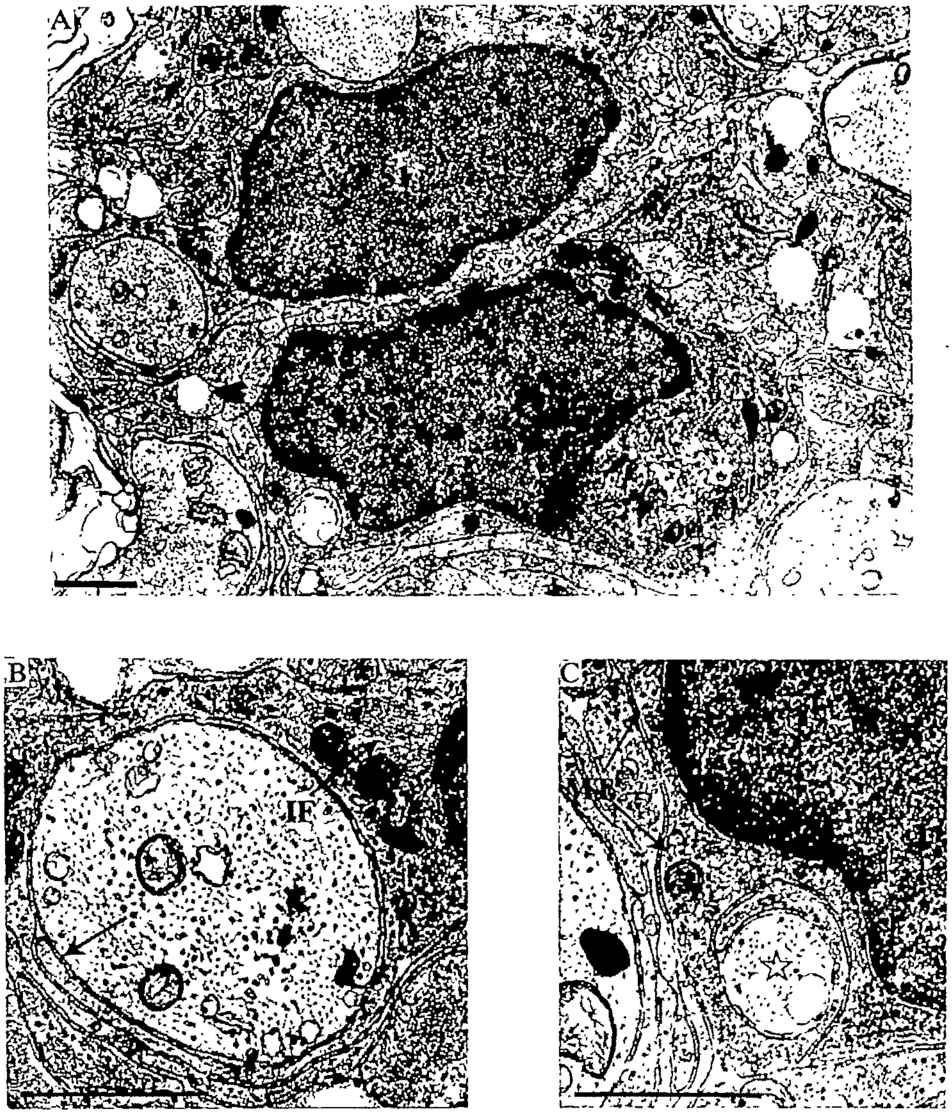

FIG. 10. A, electron micrographs of two 'dark' SGCs (S1 and S2) in a late premyelinative lesion at 12 days postinjection comprising electron-dense nuclei and axon wrapping cytoplasm. Bar = 1 μm. B, detail of SGC S1 (antigenic phenotype $Vim^+/GFA^-/GC^+$) showing copious intermediate filaments in the perinuclear cytoplasm but an intermediate filament-free tongue (arrow, lower left) which has completed a single wrap of the adjacent axon. Bar = 1 μm. C, detail of SGC S2 (antigenic phenotype $Vim^-/GFA^-/GC^+$) showing microtubules but not intermediate filaments in the perinuclear cytoplasm. The process surrounding the small axon (star) is morphologically similar to that of SGC S1. Bar = 1 μm.

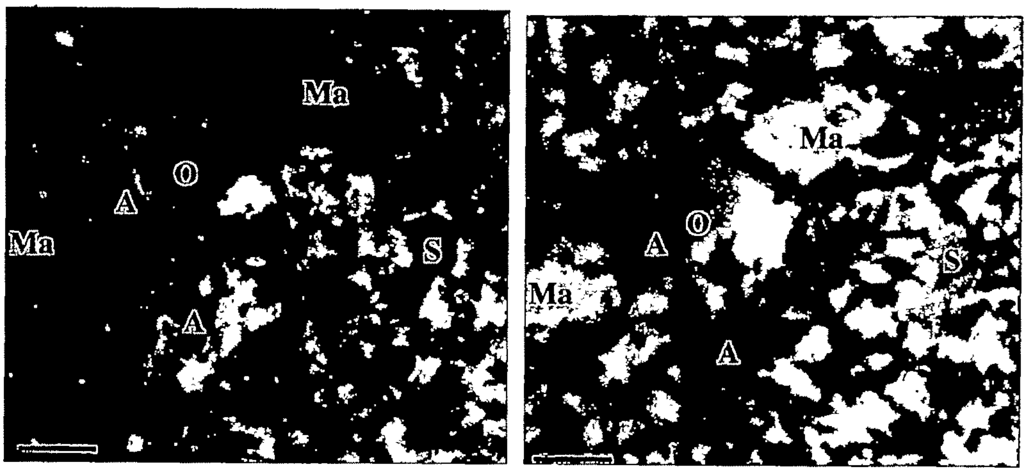

FIG. 11. Matching pair of photomicrographs of an early remyelination field at 17 days postinjection immunostained by anti-GC and anti-GFAP, respectively. With anti-GC (*left*) strong perinuclear reaction product (GC$_2$) can be seen in the newly differentiated oligodendrocyte (O) while a nearby SGC (S) exhibits typical process-only reaction product (GC$_1$) and both are GFA$^-$. The two astrocytes (A) situated adjacent to and below the oligodendrocyte (O) are GC$^-$ but GFA$^+$. Note the 2 macrophages (Ma) filled with GC$^+$ myelin breakdown product. Bars = 5 μm.

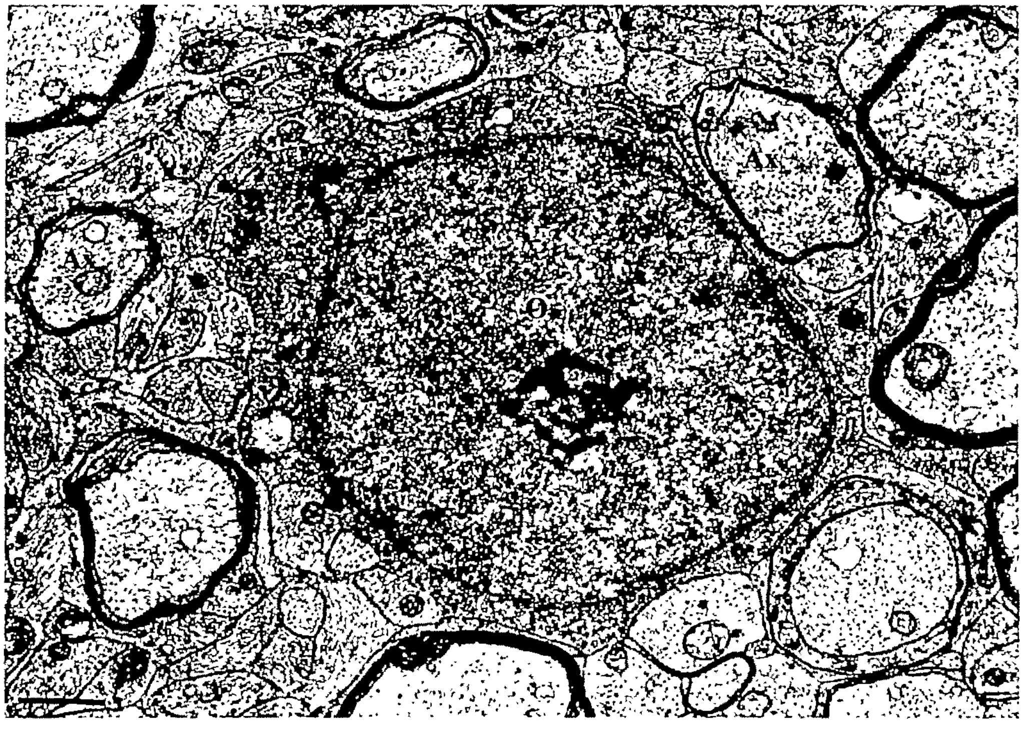

FIG. 12. Electron micrograph of a typical remyelinating oligodendrocyte (O) at 24 days postinjection (antigenic phenotype Vim$^-$/GFA$^-$/GC$^+$) surrounded by thinly myelinated axons (Ax). Bar = 1 μm.

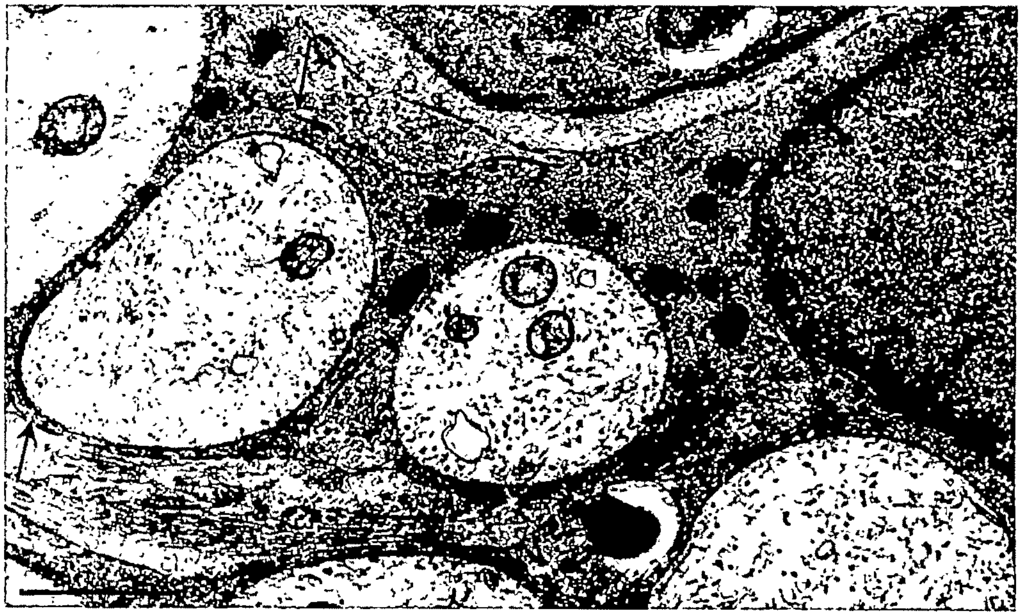

FIG. 13. Electron micrograph of a 'dark' SGC (S; antigenic phenotype $Vim^+/GFA^-/GC^+$) with an electron-dense nucleus and intermediate filament-packed cytoplasm extending tentacle-like processes (arrows) to invest nearby axons but which are not continuous with myelin. Bar = 1 μm.

axons with up to 12 lamellae of compact myelin. Throughout this 10 day period, remyelination was always by young oligodendrocytes (GC_2 cells; fig. 10). Although more and more GC_1-SGCs came to look oligodendrocyte-like with dark nuclei and electron-dense cytoplasm extending as tentacle-like processes to invest numerous nearby axons (fig. 13), these intermediate filament-rich processes were never continuous with myelin. However, there was an apparent correlation between the extent to which a process wrapped an axon and the distal extension of the intermediate filaments in that process. Before completing a single encirclement, the tips of processes often contained intermediate filaments, but once encirclement was completed they were usually only evident in the more proximal portion of the processes (fig. 10B). At 14 and 17 days postinjection, the GC_1 cells still formed the majority of the total SGC population, but by 24 days this had been reversed (fig. 6, Table) and the majority were now clearly GC_2 oligodendrocytes (figs 11, 12). The $GFAP^+$ glial cells acquired characteristics typical of mature astrocytes over the remyelination period but their total numbers remained elevated (fig. 6).

The interaxonal glial matrix also developed a more mature and normal pattern of antigenic staining. The numbers of Vim^+ periaxonal rings and straight processes decreased and the former were no longer present by 24 days. Over the same time GFA^+ staining also decreased from interaxonal locations, becoming confined to mainly straight profiles. GC^+ periaxonal rings surrounded all axons and GC staining was also present in some straight profiles, but MBP was confined to myelin sheaths.

Lesion fringe and background

Except for the earliest times studied (2 and 3 days), very little alteration to normal glial cell numbers, morphology or antigenic expression was observed either immediately surrounding or more distant to the lesion. At 2 and 3 days a few oligodendrocytes adjacent to the lesion showed reactive changes, including marked nuclear and cytoplasmic hypertrophy and enhanced cytoplasmic GC^+ staining.

DISCUSSION

Except for the oligodendrocyte toxin cuprizone and the present model, most experimental models of CNS demyelination follow a protracted time course and result in incomplete remyelination. In the present lesion of focal optic nerve demyelination, all oligodendrocytes are initially destroyed leaving only the residual astrocytes, and yet in just under 4 weeks a new population of small glial cells (SGCs) appears which become remyelinating oligodendrocytes and almost all axons are remyelinated.

In considering the origin of the remyelinating oligodendrocytes in this particular experimental model, it is appropriate to canvass the various possibilities. Endogenous sources include surviving oligodendrocytes, resting progenitor cells and dedifferentiated astrocytes, while possible exogenous sources comprise migratory oligodendrocytes and/or oligodendrocyte precursors. Surviving oligodendrocytes can be excluded, as despite careful study of the 2–3-day-old lesions no surviving oligodendrocytes were found, and before 12 days postlesion no cells with the immunocytochemical or ultrastructural features of oligodendrocytes were ever seen. Myelin and oligodendrocyte destruction is complete within the sharply demarcated borders of the lesion, glial cell numbers fall to just under half the normal total population and the residual glial cells are all large GFA^+ reactive astrocytes. Nor is there yet any evidence to support migration of exogenous oligodendrocytes. Our analysis of cellular events at the lesion periphery did not show increased numbers of oligodendrocytes at any time-point, and the autoradiographic studies did not identify dividing oligodendrocytes in this peripheral region, in contrast to the observation by Ludwin (1984) of oligodendrocyte division remote from an experimental traumatic lesion. Oligodendrocyte transformation in the region surrounding the lesion was confined to reactive features in a few otherwise mature oligodendrocytes (Carroll *et al.*, 1987) similar to the changes described by Blakemore (1972) and Arenella and Herndon (1984) in experimental demyelination induced by cuprizone and lysolethicin, respectively. Similarly, no other likely immigrant glial cells, such as small Vim^+ cells, were identified in the surrounding optic nerve to support an exogenous source of migratory precursors, despite the observations of considerable migratory capacity of oligodendrocyte precursors in the developing rat optic nerve (Small *et al.*, 1987) and after transplantation in dysmyelinated mutant mice (Lachapelle *et al.*, 1983, 1984). Finally, the pattern of uniform remyelination throughout the lesion, rather than a centripetal advancement, also implies an endogenous origin for the remyelinating oligodendrocytes. What then is the evidence for the two remaining possible endogenous sources, namely dedifferentiation of residual astrocytes or resting progenitor cells, and can those two possibilities be reliably distinguished?

Evidence suggesting that the new population of remyelinating oligodendrocytes may derive from the residual astrocyte population is as follows. First, residual astrocytes are the only glial cells identified in the early lesion and although we were unable to characterize them as either type 1 or the type 2 astrocyte of Raff *et al.* (1983) with the monoclonal A2B5 antibody (Eisenbarth *et al.*, 1979; Raff *et al.*, 1983) using our standard technique (*see* Methods), in the rodent optic nerve, with the exception of subpial astrocytes almost all are type 2 (Miller and Raff, 1984) and they share a common origin with the oligodendrocyte lineage (Raff *et al.*, 1983, 1984). Furthermore, these two cell types made complementary contributions to saltatory conduction, oligodendrocytes forming the myelin internodes and the type 2 astrocytes the perinodal apparatus (ffrench-Constant and Raff, 1986*b*; Waxman and Black, 1984). Secondly, the residual astrocyte population exhibits a number of changes suggesting dedifferentiation as previously described (Carroll *et al.*, 1987) and many of these also undergo mitosis (fig. 5). Ultrastructurally, their size increases, the cytoplasmic organelles become less organized and they lose mature astrocyte differentiation characteristics. Immunocytochemically, by 3–4 days postinjection some have an altered antigenic phenotype coexpressing GC and Vim in addition to GFA (Carroll *et al.*, 1987; fig. 4). Finally, immediately after these large reactive astrocytes begin to divide at 4–5 days, a new population of small glial cells appears (fig. 7) and by 6–7 days postinjection the total glial cell population has doubled (fig. 6, Table). Thus there is circumstantial evidence to suggest that the small glial cells (SGCs) are generated by the division of dedifferentiated type 2 astrocytes. However, the possibility of an independent origin of these SGCs from a small and as yet undetected pool of resting progenitor cells cannot be excluded completely, although to date we have not seen precursor-like cells resembling glioblasts (Sturrock, 1976) or O-2A progenitors (Raff *et al.*, 1983) in the normal optic nerve nor evidence of small glial cells dividing at 4 or 6 days postinjection.

What appears certain, however, is that the remyelinating oligodendrocytes develop from the SGC population. Between 6 and 7 days postinjection when the first of these cells are present in low numbers and 14 days when widespread remyelination begins, the SGC population continues to increase and undergoes ultrastructural and immunocytochemical maturational transformation, culminating in the appearance of remyelinating oligodendrocytes. These first simple SGCs are therefore of considerable importance as the earliest identifiable precursors in the histogenesis of the remyelinating oligodendrocyte and they may be the equivalent of the 'glioblast' described in the developing (Privat and Leblond, 1972; Skoff *et al.*, 1976; Sturrock, 1976) and adult (Arenella and Herndon, 1984; McCarthy and Leblond, 1988) CNS or the O-2A progenitor cell of the rodent optic nerve (Raff *et al.*, 1983, 1985; ffrench-Constant *et al.*, 1986*a*). Although there has only been limited ultrastructural description of the O-2A progenitor cell, apart from it having a bipolar morphology in culture with small amounts of cytoplasm (Raff *et al.*, 1984, 1985), descriptions of 'glioblasts' commonly stress a small oval nucleus with scant cytoplasm and few organelles. The small size and $GFAP^-/GC^-$ antigenic phenotype of these first SGCs accounts for their being overlooked in our preliminary study of this lesion (Carroll *et al.*, 1987) in which the antigenic markers were restricted to GFAP and GC. The lack of a detailed EM and immunocytochemical correlation in that earlier study also facilitated the assumption that the extensive interaxonal matrix of processes containing intermediate filaments which subsequently developed was derived solely from the GFA^+/GC^+ processes of dedifferentiated astrocytes. The present protocol, however, identified the SGCs per se, distinguished the intermediate filament-containing processes of these cells from those of the reactive astrocytes and traced their differentiation to oligodendrocytes.

By 7 days and onwards all SGCs had developed processes and were well endowed with organelles including intermediate filaments. Through this early premyelination phase these processes increasingly encircled and wrapped the demyelinated axons. However, as many processes emanating from astrocytes were similarly deployed, the SGCs could not be distinguished on morphology alone since both cell types contained intermediate filaments and microtubules. In our preliminary study (Carroll *et al.*, 1987) the twin observations that all glial cells present before the appearance of myelin-bearing oligodendrocytes contained intermediate filaments and that increased numbers of $GFAP^+$ cells, some with long $GC^+/GFAP^+$ processes, were followed by the appearance of GC^+/GFA^- cells concurrent with remyelination were originally interpreted as evidence of a direct astroglial origin for all these processes. The addition of anti-Vim to the immunocytochemical panel of antigenic markers in the present study, however, clearly confirmed that the intermediate filaments in these process-bearing SGCs were in fact composed of vimentin and not GFAP. The unequivocal absence of GFAP in these cells throughout the premyelination phase enabled them to be distinguished from the astrocytes. Vim^+ intermediate filaments remained a prominent feature of SGCs despite an increasingly oligodendrocyte-like appearance, behaviour and process positivity for GC. While the presence of intracytoplasmic intermediate filaments conflicts with all other descriptions of premyelinating cells in the literature (Blakemore, 1978; Ludwin, 1978; Arenella and Herndon, 1984; Raine *et al.*, 1987), the presence of the protein vimentin in glial cells is considered to be a feature of immaturity (Dahl *et al.*, 1981; Schnitzer *et al.*, 1981; Herpers *et al.*, 1986) and Raff *et al.* (1984) have described Vim^+ staining in the O-2A progenitor cells persisting until oligodendrocyte differentiation has been completed. Therefore, the absence of any glial cells without intermediate filaments in the lesion in the premyelination phase, the intimate investment by processes of SGCs of demyelinated axons and the coexpression of GC in those same processes (GC_1 phenotype) presaged their density of oligodendrocyte differentiation. Not until remyelination began (between 12 and 14 days) did cells appear containing only microtubules, having myelin-forming processes (fig. 12) and a GC_2 phenotype ($Vim^-/GFA^-/GC^+$; fig. 11). Even these oligodendrocytes were indistinguishable from the dark GC_1 SGCs with LM or low power EM, but the combination of immunocytochemistry and high resolution EM clearly identified them. Finally, the steady progression of the inverse relationship between the numbers of GC_1 and GC_2 phenotypic cells as myelination proceeded, completes the argument for the differentiation from one to the other (fig. 6).

Although the timing of intracellular events in vivo is more difficult than in vitro, the expression of the ultrastructural and immunocytochemical features of oligodendrocytes in the SGCs over a short period of time implies a fairly rapid completion of what appears to be distally-commencing differentiation. From high resolution EM observations it seems possible that the GC_1-SGCs differentiate into myelin forming, intermediate filament-negative GC_2 oligodendrocytes as a result of signals related to the degree of axonal wrapping. No SGCs containing intermediate filaments were seen to be continuous with processes making more than one complete wrap around an axon. On the other hand, SGC processes which had completely encircled an axon were often intermediate filament-free and indistinguishable from oligodendrocyte tongues, yet remained continuous with perikarya still containing intermediate filaments.

In this model of CNS demyelination, the remyelinating oligodendrocyte is derived from a new population of small glial cells (SGC). They first resemble glioblasts, then an immature glial cell that finally differentiates to become a myelinating oligodendrocyte. Although the evidence from this study suggests that the SGCs in turn may be derived from dedifferentiated astrocytes, their possible origin from as yet unidentified preexisting or immigrant progenitor cells cannot be dismissed completely, and is the subject of on-going investigation.

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VISUAL LOSS IN MULTIPLE SCLEROSIS AND ITS RELATION TO PREVIOUS OPTIC NEURITIS, DISEASE DURATION AND CLINICAL CLASSIFICATION

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SUMMARY

Visual function was investigated in a group of 58 clinically classified cases of multiple sclerosis (MS). Psychophysical measures of luminance and chromatic threshold sensitivity and temporal contrast sensitivity were undertaken, together with visual evoked potentials and Bjerrum screen perimetry. The patient group was divided on the basis of optic neuritis (ON), clinical disease duration and clinical classification. A comparison of the results of all visual measures suggested a nonuniform loss of function in the patient group without ON and a more consistent loss of function in the group with ON. The various measures were equally efficient in detecting abnormal function, albeit from different areas of the central visual field. Clinical disease duration was not a significant independent factor in predicting visual dysfunction. In contrast, a comparison of clinical classification categories revealed significantly fewer abnormalities of visual function in the suspected MS category (31%) than in the ON, early probable and clinically definite categories (75–100%), a result which indicated the importance of clinical classification as a predictor of visual dysfunction.

INTRODUCTION

The anterior visual pathways are affected in almost all cases of clinically definite multiple sclerosis (MS) examined at postmortem (Lumsden, 1970; Ulrich and Groebke-Lorenz, 1983). During life, abnormalities of the visual pathway have been detected in a high proportion of clinically definite MS and optic neuritis (ON) patients by means of a variety of experimental techniques, including visual evoked potentials (VEPs) (Halliday *et al.*, 1973; Wright *et al.*, 1987), psychophysical measures (Heron *et al.*, 1974; Regan *et al.*, 1977; Hess and Plant, 1983) and visual fields (Patterson and Heron, 1980; Meienberg *et al.*, 1982). In cases of suspected MS, with a single clinical episode of neurological dysfunction, abnormalities of visual function have been found in a much smaller

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Blumhardt *et al.* (1982) studied undiagnosed progressive spinal cord disease and found that the VEP abnormality rate increased from 10% to 36% between subacute and chronic cases with a symptom duration of more than 3 yrs. However, Patterson and Heron (1980), in their visual field study, detected a field defect in 81% of cases with possible MS with a mean duration of 2 yrs. The role of psychophysical measures in determining the extent of visual loss in suspected MS has not been investigated systematically because the McAlpine (1972) category of possible MS used previously excludes isolated clinical episodes, except for progressive paraplegia.

In the present study, visual function was assessed by psychophysical measures made at the fovea, including sensitivity to stimuli selective for luminance and chromatic function and sensitivity to temporal contrast (the de Lange attenuation characteristic; de Lange, 1958), together with VEPs and Bjerrum screen visual fields. Two groups of MS patients were examined: a 'first attack' group, investigated as soon as possible after the clinical onset of the disease, and a group of MS cases of longer duration. The study had two aims: first to assess the pattern of visual loss in cases with and without ON and, secondly, to examine abnormalities of visual function in relation to clinical disease duration and clinical classification. Preliminary reports on some aspects of this study have appeared in abstract form (Honan *et al.*, 1987; Edgar *et al.*, 1988).

METHODS

Luminance and chromatic threshold

Psychophysical measures were performed with a modified visual perimeter, with the stimulus located centrally in the field. The system, which was controlled by a laboratory microcomputer, was similar to that described previously (Foster *et al.*, 1985). The subject was seated in a chair with a firm headrest, 1.2 m from the perimeter screen. An artificial pupil was not used. The test was performed monocularly; the other eye was occluded by a patch. Patients were examined for refractive errors and either wore their own spectacles or a suitable lens was inserted into an eyepiece in front of the eye. The circular stimulus flash, of angle subtense 0.25°, duration 200 ms, selected spectral content (either white, correlated colour temperature 3250 K, or red, cut-on wavelength 622 nm) and variable luminance, appeared superimposed on a steady, concentric, uniform white (correlated colour temperature 3250 K) auxiliary field, of luminance 1.85 log $cd \cdot m^{-2}$ and variable subtense (either 0.25° or 1.25°); an additional, steady, concentric, uniform white conditioning field, luminance 1.42 log $cd \cdot m^{-2}$ and subtense 20°, was introduced to maintain a constant state of retinal adaptation. The stimulus and conditioning fields were both derived from a tungsten-halogen light source. The subject controlled initiation of the stimulus using a push-button box connected to a laboratory microcomputer.

To assess luminance and chromatic sensitivity, four separate stimulus conditions were employed in which a red or white flash was presented on either the large or small (spatially coincident) auxiliary field. Previous studies (Foster, 1981; Foster and Snelgar, 1983; Foster *et al.*, 1985) had shown that the white flash on the large auxiliary field ('white large' experimental condition) yielded a luminance threshold and the red flash on the small auxiliary field ('red small' experimental condition) yielded a chromatic threshold. (The other conditions provided control data, which are not reported here as they were similar to those of previous reports, e.g., Foster *et al.*, 1985.)

The subject was given practice trials before each of the four separate experimental conditions and was instructed to respond (forced choice) 'yes' or 'no' according to whether the stimulus was seen or not. The threshold for each experimental condition was based on 45 stimulus trials, including 5 randomly placed 'empty' trials, containing no stimulus light. The empty trials were inserted to assess subject bias. The luminance level of the stimulus was adjusted by the microcomputer during each trial sequence using a hybrid adaptive technique (Taylor and Creelman, 1967; Hall, 1981). The time taken to complete the trial sequence for each experimental condition was 5–10 min. Response scores as a function of stimulus luminance were analysed using a computer-based method which fitted a cumulative gaussian frequency-of-seeing curve to each set of data (Foster and Bischof, 1987). The stimulus threshold was defined as the level at which the stimulus was seen on 50% of trials.

de Lange attenuation characteristic

Temporal contrast sensitivity was determined using an arrangement of stimulus and background fields in which the 0.25° stimulus had a sinusoidal temporal profile and appeared within a fixed, contiguous surround field (inner diameter 0.25°, outer diameter 1.25°), of luminance 2.0 log $cd \cdot m^{-2}$. The stimulus and surround fields were produced by yellow light-emitting diodes (peak emission wavelength 584 nm, half-height bandwidth 26 nm), driven by a digital electronic system under the control of the microcomputer. The large conditioning field was identical to that used in the luminance and chromatic thresholds measurements. The luminance $L(t)$ of the stimulus varied as a function of time, t, according to the relationship $L(t) = a + b \cdot \cos(2\ ft)$, where a was the mean (d.c.) light level, b was the modulation depth, normally expressed as a percentage of the mean a, and f was the temporal frequency. The total duration of the stimulus was 2 s.

The subject was again given preliminary practice trials. The temporal frequency was held constant at 8 Hz, the modulation depth of the stimulus was varied, and the subject was instructed to say 'yes' or 'no' according to whether the stimulus appeared to be flickering or steady. The temporal frequency was then set to 2 Hz, the first of the range of values to be tested. A temporal contrast threshold was obtained by varying the modulation depth over 30 stimulus trials according to the adaptive technique described earlier. Five 'empty' trials, in which the stimulus had the constant luminance value b, were again inserted to assess subject bias. This whole sequence of trials lasted about 5 min. Temporal contrast thresholds were determined at temporal frequencies increasing in 3 Hz increments, up to 29 Hz or until a threshold could no longer be recorded because the stimulus appeared not to flicker even at maximum modulation depth. At the end of this series of measurements, the temporal contrast threshold at 2 Hz was redetermined to test for possible fatigue or practice effects. The data were analysed using the same computer-based method described above (Foster and Bischof, 1987).

Visual evoked potentials

Pattern reversal VEPs were measured by a conventional technique. The checkerboard stimulus was generated by a Medelec Sensor ST10, displayed on a Hitachi television screen and the time-locked responses were recorded with a Medelec Sensor ER94a averager. The pattern was reversed at 2 Hz. The test was performed monocularly, the other eye being lightly occluded with an eyepatch. The subject was seated 1.7 m from the screen. The stimulus field subtended 12° horizontal by 9° vertical at the subject's eye; the check size was 48 min arc. The luminance of the dark squares was 1.29 log $cd \cdot m^{-2}$ and of the white squares 2.86 log $cd \cdot m^{-2}$.

Visual fields

A Bjerrum screen was used to plot visual fields, after the method of Patterson and Heron (1980), where the criteria for detection are defined. The average screen luminance was 0.53 log $cd \cdot m^{-2}$ and the luminance of the white targets was 2.25 log $cd \cdot m^{-2}$.

Patients

Fifty-eight patients were entered into the study and were divided in two ways, yielding groups according to clinical disease duration and visual history. Additional details concerning Snellen acuity and pallor of the optic disc are given in the Results section.

Classification by disease duration. Group A, the 'first attack' group, consisted of 37 cases investigated as soon as possible after the clinical onset of the disease; the mean duration ± SD was 7.1 ± 4.8, range 0.25 − 14 months. Group B consisted of 21 MS cases of longer duration with a mean of 95 ± 64, range 19 − 228 months. The large variation in disease duration in group B was introduced deliberately to assess the effect of this variable. The patients were classified using the clinical criteria of McDonald and Halliday (1977), although isolated ON was also accepted as a separate diagnostic category. The number of cases in each category is shown in Table 1. Group A contained 11 males and 26 females; mean age was 33.3 ± 8.5, range 20 − 50 yrs. Group B contained 4 males and 17 females; mean age was 34.8 ± 5.4, range 22 − 46 yrs.

Classification by visual history. Patients were reclassified as follows. Group 1 consisted of 29 patients without ON, and group 2 of 29 patients with ON. For cases in group A, the mean duration from the last episode of ON was 5.3 ± 4.5, range 0.25 − 12 months; for cases in group B, mean duration from the last episode of ON was 56.8 ± 55.4, range 6 − 168 months. Therefore both groups consisted mainly of cases which had passed the acute phase (first 6 wks) and were, with respect to duration, comparable with previous follow-up ON studies (Nikoskelainen, 1975).

TABLE 1. CLINICAL CLASSIFICATION*

*Group A***		*Group B***	
MS category		MS category	
Suspected	15	Early probable	6
Optic neuritis	7	Clinically definite	15
Progressive possible	1		
Progressive probable	2		
Early probable	12		
Total	37		21

* Based on the McDonald and Halliday (1977) criteria. ** Group A = first-attack cases; group B = longer-duration MS cases. The number of cases in each category is shown.

A control group of 33 healthy volunteers participated in the psychophysical measures. There was no significant difference between control and patient groups for age (t = 1.187, df = 89, n.s.) or sex (χ^2 = 1.112, df = 1, n.s.). For VEP measurements, a separate control group of 22 healthy volunteers was used which was also well matched to the patient group for age and sex.

Patients were tested in three separate sessions, each lasting 1 − 1.5 h. The first contained the clinical assessment and measurement of visual fields and VEPs. Luminance and chromatic thresholds were measured in the second session and the de Lange attenuation characteristic in the third. The three sessions were usually spread over 2 successive days, to reduce subject fatigue. The sessions were not always performed in the same order. Because of the time-consuming nature of the experimental protocol, visual function was assessed in one eye only. A few patients, because of personal or professional commitments, were unable to attend all sessions.

Statistical analysis

The majority of the statistical analyses involved comparisons of mean threshold levels or VEP latencies, and independent t tests, with pooled estimates of variance, were used. Two-tailed tests were applied, with P values classified as not significant (n.s.) for $P > 0.05$. Where appropriate, mean values and 95% confidence intervals (CIs) were computed. The Mann-Whitney U test was used for data on ordinal scales, and for comparison of clinical disease durations, which were positively skewed. The χ^2 test was used for data on nominal scales. The Pearson correlation coefficient was used to quantify the relationship between duration and measures of visual function.

RESULTS

Effect of optic neuritis

Clinical details. Snellen acuity was impaired, relative to the control group, in both group 1, without ON, median acuity 6/6, range 6/4–6/9 (U = 296, n_1 = 29 n_2 = 33, $P < 0.01$) and in group 2, with ON, median acuity 6/9, range 6/5 to greater than 6/60 (U = 141, n_1 = 29 n_2 = 33, $P < 0.001$). Snellen acuity was also significantly more impaired in group 2 than group 1 (U = 214, $n_1 = n_2 = 29$, $P < 0.001$). An afferent pupillary defect occurred in 6/27 cases in group 1 and 13/27 cases in group 2. Pallor of the optic disc was present in 6/28 cases in group 1 and 15/28 cases in group 2. Visual field defects occurred in 9/24 cases in group 1; 5 cases with arcuate scotomata, 2 cases with focal constriction and 2 cases with general peripheral constriction. In group 2, visual field defects occurred in 16/27 cases; 8 cases with central or paracentral scotomata, 5 cases with arcuate scotomata and 1 case each of sector defect, focal constriction and general peripheral constriction respectively.

Psychophysical measures. The luminance and chromatic threshold results are shown graphically in fig. 1A. The mean and 95% CI for control and patient groups are shown. In group 1, without ON, the mean increase in threshold, compared with the control group, for the white large (luminance) condition was 0.22 log $cd \cdot m^{-2}$ (t = 1.954, df = 48, n.s.) and for the red small (chromatic) condition was 0.18 log $cd \cdot m^{-2}$ (t = 2.761, df = 48, $P < 0.01$). In group 2, with ON, the mean increase in threshold for the white large condition was 0.62 log $cd \cdot m^{-2}$ (t = 4.161, df = 53, $P < 0.001$) and for the red small condition was 0.71 log $cd \cdot m^{-2}$ (t = 3.908, df = 52, $P < 0.001$). Therefore, relative to the control group, each patient group showed approximately equal mean losses of luminance and chromatic sensitivity and the losses were highly significant in the group with ON. This result confirms and extends the findings previously reported from this laboratory on a smaller group of ON cases (Foster *et al.*, 1985). In addition, losses in group 2 were significantly greater than in group 1, both for the white large condition (t = 2.186, df = 51, $P < 0.05$) and the red small condition (t = 2.733, df = 50, $P < 0.01$).

The de Lange attenuation characteristic results are shown graphically in fig. 1B. Mean threshold modulation depths and 95% CI for control and patient groups are shown at each temporal frequency. The mean differences (d) between the 2 Hz thresholds obtained at the beginning and end of the sessions for the various groups were as follows: control group d = 0.02 log percent (t = 0.478, df = 26, n.s.); group 1 d = 0.03 log percent (t = 0.939, df = 24, n.s.); group 2 d = 0.04 log percent (t = 0.302, df = 26, n.s.). The differences were very small, confirming that no significant practice or fatigue effects occurred.

In group 1, without ON, there were small, relatively uniform, mean reductions in temporal contrast sensitivity of 0.05–0.12 log percent relative to the control group; these small losses of function were not statistically significant. In group 2, with ON, there were statistically significant mean reductions, relative to the control group, in temporal contrast sensitivity of 0.29–0.37 log percent (t ≥ 4.026, df = 55, $P < 0.001$)

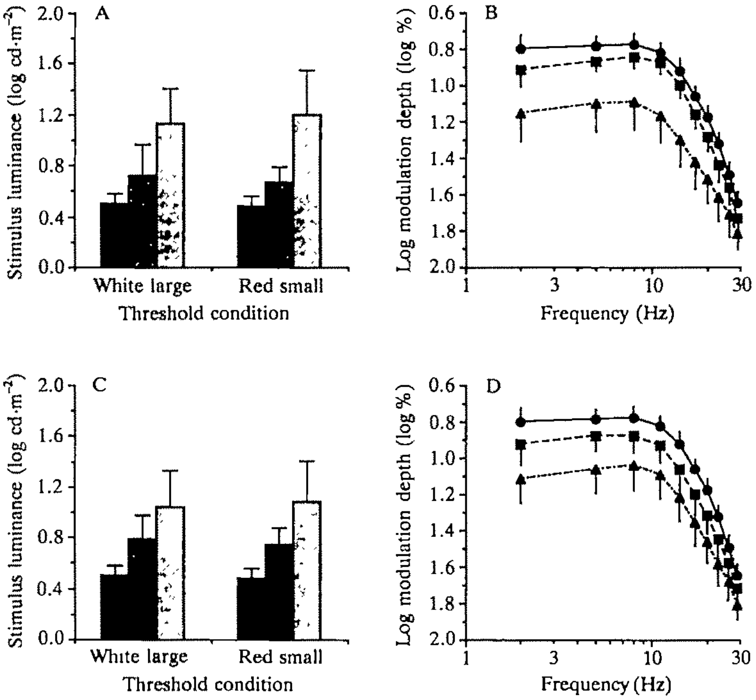

FIG. 1. Mean threshold values and 95% confidence intervals for control and patient groups. The results for patients with and without ON are shown in (A) for luminance and chromatic thresholds, and in (B) for the de Lange attenuation characteristics. The results for patients in group A (first-attack) and group B (longer-duration MS) are shown in (C) for luminance and chromatic thresholds, and in (D) for the de Lange attenuation characteristics. In A, C, filled columns = controls; hatched columns = patients without ON; dotted columns = patients with ON. In B, D, filled circle = controls, filled square = patients without ON; filled triangle = patients with ON.

at all temporal frequencies from 2 to 23 Hz; at 26 and 29 Hz, the mean differences decreased slightly but remained significant ($t \geq 3.103$, $df = 54$, $P < 0.01$) (compare Hess and Plant, 1983; Wright *et al.*, 1987). This pattern of loss was similar to that reported by Edgar *et al.* (1990) in the fovea of patients with ON, although there were differences in the level of statistical significance.

Visual evoked potentials. In group 1, without ON, the mean increase in latency relative to the control group was 7.0 ms ($t = 2.102$, $df = 48$, $P < 0.05$). In group 2, with ON, the mean increase in latency relative to the control group was 27 ms ($t = 5.085$, $df = 47$, $P < 0.001$). The increase in latency of 20 ms for group 2 relative to group 1 was also significant ($t = 3.865$, $df = 53$, $P < 0.001$).

Comparison of individual values. As expected, the psychophysical, VEP and Bjerrum screen visual measures revealed abnormalities of function in the patient groups, both with and without ON. To assess these measures from the standpoint of diagnostic efficiency, a comparison of abnormal results for individual cases was made. It should be noted, however, that the measures assessed different aspects of visual function over different, but overlapping, regions of the central visual field: psychophysical measures from the central 0.25° diameter region, VEPs from the central 12°×9° region, and Bjerrum screen fields from the central 50° diameter region. For both psychophysical and VEP measures, the normal range was defined as the mean ± 2 SD of the control group. The number of abnormal cases for each individual visual measure is shown in Table 2.

TABLE 2. COMPARISON OF INDIVIDUAL ABNORMALITIES FOR THE DIFFERENT VISUAL MEASURES IN CASES WITH AND WITHOUT OPTIC NEURITIS*

	Group 1 *(without ON, n = 19)*	*Group 2* *(with ON, n = 26)*
Visual measure		
Visual field	6	16
Luminance and chromatic thresholds	7	19
de Lange attenuation characteristic	5	15
Visual evoked potentials	4	20
Cases with at least one abnormal measure	14	24

* Only cases in which all measures were performed are included. The number of abnormal cases in each category is shown.

In group 1, without ON, 14/19 cases had at least one abnormal value. Results for each individual measure, however, showed a much lower proportion of abnormal cases, with no single measure being more sensitive than the others ($\chi^2 = 1.23$, df = 3, n.s.). This variation in proportions of abnormal results can probably be attributed to the patchy character of the demyelination. Psychophysical and VEP measures were recorded from overlapping areas, and in principle may have involved the same affected fibres but, in all 5 cases in which an isolated visual field abnormality occurred, it was an arcuate scotoma located at more than 10° eccentricity from the fovea and thus outside the test region of the other measures. Insofar as comparisons can be made over different measures and different areas of the visual field, the findings were broadly consistent with Regan *et al.* (1976), who also reported a patchy abnormality of visual function, particularly in cases of spinal MS.

In group 2, with ON, 24/26 cases had at least one abnormal visual measure. Again, no single visual measure was more sensitive than the others ($\chi^2 = 2.97$, df = 3, n.s.). The proportion of abnormal cases was much greater than in group 1 and the distribution of abnormal values was more uniform. There were no cases with isolated arcuate scotomata, suggesting a more consistent loss of function in the central visual field. There remained a small variation in relative sensitivity of the two psychophysical measures, although both measures were taken from the same area of the central fovea. Functional differences within the central field have been reported previously for relative perceptual latency and two-flash resolution (Galvin *et al.*, 1976; *see also* Snelgar *et al.*, 1985).

Effect of disease duration

The effect of clinical disease duration was assessed by comparing the results of the psychophysical and VEP measures for the first attack group, group A, and the longer-duration MS group, group B (*see* Table 1 for clinical classification).

Psychophysical measures. Mean luminance and chromatic thresholds and 95% CI for the control and patient groups are shown graphically in fig. 1c. Both patient groups had significantly elevated thresholds relative to the control group. There was a trend for a more severe loss of function in group A, the first-attack group, than in group B, the longer-duration MS group. However, the mean threshold differences (d) did not reach significance either for the white-large (luminance) condition, d = 0.25 log $cd \cdot m^{-2}$ (t = 1.304, df = 51, n.s.) or for the red-small (chromatic) condition, d = 0.34 log $cd \cdot m^{-2}$ (t = 1.668, df = 50, n.s.).

For the de Lange attenuation characteristic, mean threshold modulation depths and 95% CI for the control and patient groups are shown graphically in fig. 1D. There was a well defined reduction of temporal contrast sensitivity in group A, relative to the control group (over 2–23 Hz, mean difference (d) = 0.26–0.31 log percent, t ≥ 3.572, df = 60, $P < 0.001$). In group B, the loss of temporal contrast sensitivity was smaller (over 2–23 Hz, d = 0.09–0.14 log percent, t ≥ 1.820, df = 47, n.s.). As in the luminance and chromatic threshold measurements, there was a trend towards a greater loss of function in group A than in group B. Mean differences in threshold modulation depth between groups A and B from 8 to 23 Hz were between 0.14 and 0.16 log percent; these differences were not significant. At 2 Hz the mean difference was 0.19 log percent (t = 2.035, df = 51, $P < 0.05$) which, although statistically significant, probably had no physiological significance. At high frequencies the mean difference between groups A and B also decreased.

Visual evoked potentials. In group A, the mean P100 latency was 120.6 ms, 95% CI 112.9–128.3 ms; the mean increase in latency relative to the control group was 18.1 ms (t = 3.626, df = 56, $P < 0.001$). In group B, the mean P100 latency was 116.9 ms, 95% CI 107.3–126.5 ms; the mean increase in latency relative to the control group was 14.4 ms (t = 3.172, df = 39, $P < 0.01$). Again, there was a small nonsignificant trend towards a greater abnormality of function in group A, the mean difference in latency between groups A and B being 3.7 ms (t = 0.608, df = 53, n.s.).

Correlation of disease duration and visual function. The correlation analysis was undertaken on the combined patient groups. For individual patients, values for each visual measure were compared with the clinical disease duration. There was no evidence of a linear correlation between any aspect of visual function and disease duration or duration from the most recent clinical relapse. This finding cannot be explained by any difference between the groups with and without ON in respect of either disease duration ($z = 0.016$, $n_1 = n_2 = 29$, n.s.) or duration from the most recent relapse ($z = 0.770$, $n_1 = n_2 = 29$, n.s.). Thus there was no evidence that disease duration, as an independent variable, was a contributory factor in determining abnormal visual function. However, the time from the most recent episode of ON was significantly shorter in

TABLE 3. EFFECT OF CLINICAL CLASSIFICATION ON ABNORMALITIES OF VISUAL FUNCTION IN INDIVIDUAL CASES*

	Luminance and chromatic threshold (n = 53)	*de Lange attenuation characteristic (n = 53)*	*Visual evoked potentials (n = 56)*	*Total (n = 56)*
Classification				
Suspected	3 (14)	3 (13)	2 (16)	5 (16)
Optic neuritis	6 (7)	5 (7)	6 (7)	7 (7)
Early probable	9 (17)	7 (18)	13 (20)	15 (20)
Clinically definite	9 (15)	5 (15)	7 (13)	10 (13)

* The number of abnormal cases is shown together (in parentheses) with the number of cases measured in each category. The Total column represents the number of cases with at least one abnormal measure.

group A than in group B ($z = 4.229$, $n_1 = 12$ $n_2 = 17$, $P < 0.001$). The trend towards greater losses of visual function in group A can probably be explained by relative recovery in the cases of old ON in group B.

Effect of clinical classification

The effect of clinical classification was assessed by comparing the proportion of individual visual abnormalities in each diagnostic category. There was only 1 case of progressive possible MS, so this was included in the suspected MS category. Similarly, the 2 cases of progressive probable MS were included in the early probable MS category. The number of abnormal cases in the suspected MS group was 5/16, which represented the proportion of cases in which the laboratory visual measures modified the diagnosis (Poser *et al.*, 1983). The number of abnormal cases in the suspected MS category was significantly less than in the other three categories ($\chi^2 = 13.64$, df = 3, $P < 0.01$), whereas no significant difference occurred in the number of abnormal cases in the ON, early probable and clinically definite MS categories ($\chi^2 = 2.14$, df = 2, n.s.).

DISCUSSION

Classification and duration

This study supports the conclusion that clinical classification (McDonald and Halliday, 1977) is an important variable in predicting the occurrence of abnormal visual function. The suspected MS group contained 31% abnormal cases, compared with 75–100% abnormal cases in the early probable, clinically definite and ON groups. Previous VEP reports had found 5–30% abnormal suspected MS cases (Matthews *et al.*, 1977; Ormerod *et al.*, 1987); although these findings are broadly similar to the present ones, they are not directly comparable as all our measurements were obtained from one eye only in each patient. Two previous psychophysical studies (Regan *et al.*, 1976; Galvin *et al.*, 1977) reported 2/4 and 4/5 abnormal cases, respectively, in the possible MS category (McAlpine, 1972): the higher proportion of abnormal cases detected in their series may be related to the different diagnostic criteria and the very small number of cases studied.

The finding that clinical disease duration was not an important independent factor in determining abnormal visual function is at variance with some previous work. For example, Blumhardt *et al.* (1982) reported that the frequency of abnormal VEPs in cases of undiagnosed progressive spinal cord disease increased with disease duration. Ormerod *et al.* (1987) did not observe an increased frequency of VEP abnormality with duration in cases of clinically isolated spinal cord syndromes, although the phenomenon did occur with clinically isolated brainstem lesions. Two combined psychophysical and evoked potential studies are of interest in this context. Salmi (1985) compared critical flicker frequency with VEPs: the proportion of abnormalities in cases of MS or ON with a short clinical disease duration was roughly equivalent, whereas in chronic MS VEPs were more often abnormal than critical flicker frequency. Similar findings, in respect of disease duration, were reported by Lorance *et al.* (1987) in their study comparing spatial contrast sensitivity with VEPs. These psychophysical studies provide supportive evidence that perceptual aspects of visual dysfunction are not necessarily directly related to disease duration.

Some of the differences among these reports may represent a confounding effect of classification on duration. About 90% of cases of clinically definite MS have measurably abnormal visual function (Halliday *et al.*, 1973; Regan *et al.*, 1976); it is likely that with increasing disease duration, more MS cases would fall into this category. The discriminative effect of clinical classification on the probability of detecting abnormal visual function was clearly demonstrated in our series of measurements.

Distribution of lesions

It has been estimated that between a quarter and a third of fibres within the optic nerve subserve vision within 10° eccentricity of the fovea (Polyak, 1957; Potts *et al.*, 1972; Perry and Cowey, 1985). The proportion of cases with central scotomata in the ON group in this study was 8/27 (30%), similar to the 27% and 33% of cases with central scotomata detected in two large follow-up studies of ON (Nikoskelainen, 1975; Perkin and Rose, 1979). Patterson and Heron (1980) detected a high frequency of arcuate scotomata in their study of MS cases in remission. The series was later extended to 100 cases when 359 arcuate scotomata were detected, of which 56% were in the temporal field (V. H. Patterson and J. R. Heron, unpublished observations). Perry *et al.* (1984) in a study of the primate retina, indicated that the nasal retina contained 60% of the retinal ganglion cells, implying that 60% of optic nerve fibres subserved the temporal half-field.

Regan *et al.* (1976) used the term 'islands of demyelination' to describe scattered defects in visual function, particularly in spinal MS cases. A combination of scattered lesions and natural variation in nerve fibre density within the optic nerve may explain the patchy individual visual losses in the group without ON and the more uniform visual losses in the group with ON, where demyelination is likely to affect a larger proportion of the optic nerve. Ulrich and Groebke-Lorenz's (1983) postmortem study of chronic MS cases has provided some support for this view. In all cases in which a clinical episode of ON had occurred, the schematic drawings indicated that the full thickness of the nerve was affected at some point along its course. However, in the remaining optic nerves the schematic drawings showed that although some nerves showed full-thickness demyelination others were affected in patches and that no part of the optic nerve was selectively damaged.

The clinical importance of this phenomenon is highlighted by the investigation of MS cases without ON, in which a single visual measurement may not reveal abnormal function; this was apparent in our series and that of Hammond and Yiannikas (1986), who compared the usefulness of foveal and full-field VEPs and found the greatest diagnostic benefit in suspected MS.

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FROM COVERT TO OVERT RECOGNITION OF FACES IN A PROSOPAGNOSIC PATIENT

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SUMMARY

Prosopagnosia is an inability to recognize known persons as a result of a failure to access relevant memories through the inspection of their faces. The nature of this disturbance, and the fate of memories related to faces, were investigated in a long-standing prosopagnosic woman (P.V.). An examination of P.V.'s perceptual capacities indicated no major impairment at matching faces, including different views of the same faces, and multidimensional scaling analysis showed that she could achieve configurational representations of faces as do normal subjects. In spite of her inability to evoke memories of known persons from their faces, P.V. displayed clear evidence that she could use pertinent memories related to these faces in tasks that did not explicitly call for their evocation. This covert recognition of faces was observed in perceptual learning and cued-recognition tasks. Because these findings suggested preserved semantic knowledge about unrecognized faces, attempts were made at surmounting the blocked activation of pertinent memories. Some of these attempts were successful in inducing P.V. into experiencing a sense of familiarity with the faces and identifying them, and this was the first occurrence of overt face recognition by P.V. since the onset of her illness. These findings provide clarification of the nature of the prosopagnosic disturbance and new information about the processes by which faces are recognized. They suggest that (1) prosopagnosia may result from a breakdown at different levels of face-recognition processes, (2) prosopagnosia may occur in spite of normal configurational encoding of facial representations, (3) covert recognition of overtly unrecognized faces requires the integrity of perceptual processes, and (4) failure of overt face recognition reflects a disturbance in the normal interactions between pertinent memories and facial representations which thus remain meaningless.

INTRODUCTION

Prosopagnosia is a neurologically based deficit characterized by the inability to recognize known persons by their faces in the absence of severe intellectual, sensory or cognitive impairments. Functionally, it is a failure to evoke memories of these persons, precluding any sense of familiarity from the perception of their faces. It results from a breakdown in the processes normally underlying face recognition, at the level either of the extraction of the physiognomic invariants, of the memories or semantic information associated with the faces, or of the activation of these memories (Young, 1988; Damasio *et al.*, 1989). Neurologically, it is thought to be produced by bilateral damage in the occipitotemporal cortices or their forward projections, and all but one patient whose brains came to autopsy suffered from bilateral damage (Meadows, 1974; Damasio, 1985); the exception (Landis *et al.*, 1988) may not be representative of long-standing prosopagnosia as the patient died within 10 days of symptom onset.

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While the diagnosis of prosopagnosia is typically based on an absence of a feeling of familiarity with faces of known individuals and on a failure of overt recognition of these faces, recent evidence indicates that the processing of familiar faces and their recognition are still taking place outside the patient's realm of awareness. This is suggested by physiological and behavioural indices of recognition showing significant differences in response to familiar and unfamiliar faces. For instance, Bauer (1984, 1986) reported autonomic (electrodermal) discrimination between correct and incorrect face-name matches, and Tranel and Damasio (1985, 1988) found autonomic responses to the presentation of familiar faces that patients failed to recognize overtly but not to unfamiliar faces. Behavioural evidence of covert recognition comes from patterns of semantic facilitation and interference produced by unrecognized faces of familiar persons in learning and priming tasks (Bruyer *et al.*, 1983; De Haan *et al.*, 1987; Young and De Haan, 1988). Because the familiar/unfamiliar distinction depends on whether pertinent memories of faces have been accessed, these findings suggest that some discrimination of faces can still be achieved. Prosopagnosics thus appear to possess implicit knowledge of faces that they cannot recognize overtly, and their brains still perform operations by which a given face activates pertinent memories, but the outcome of these operations fails to reach consciousness.

Although the occurrence of covert face recognition in prosopagnosics is now well established, it is not observed in all patients. For instance, Bauer (1986) found that correct face-name matches failed to elicit electrodermal responses in one patient (G.Y.) who was described as suffering from 'apperceptive' agnosia. Similarly, Newcombe *et al.* (1989), Sergent and Villemure (1989) and Young and Ellis (1989) described patients who displayed no evidence of semantic facilitation in priming and learning tasks that yielded positive results in other prosopagnosics. Individual differences between patients in their structural damage and functional disturbance are the likely source of these discrepancies, and a characterization of the conditions underlying the occurrence of covert face recognition could provide a clearer specification of the prosopagnosic deficit. The phenomenon of covert recognition of overtly unrecognized faces thus offers a new avenue to the study of prosopagnosia and to the understanding of the neurobiological basis of cognition and its functional organization. The present study further examined this issue in a long-standing prosopagnosic patient who displayed strong evidence of covert face recognition. It addressed three main questions.

1. Does the occurrence of covert recognition depend on the functional nature of the prosopagnosic disturbance? This has been hypothesized by Bauer (1986), Newcombe *et al.* (1989) and Sergent and Villemure (1989) and would be consistent with earlier suggestions (e.g., Hécaen, 1981; De Renzi, 1986) that there are at least two types of prosopagnosia, one primarily characterized by a perceptual impairment and the other essentially reflecting a memory deficit. However, the actual mechanism preventing or permitting covert recognition of faces remains unspecified and this question was examined in the present study by comparing the patient's perceptual capacities with those of another prosopagnosic who displayed no sign of covert recognition and whose disturbance was primarily perceptual (Sergent and Villemure, 1989).

2. What does the failure or success of covert face recognition tell us about the nature of prosopagnosia? Given the accumulation of empirical data on covert recognition, some trends concerning the occurrence of this phenomenon will be outlined with respect to its functional and neurological basis.

3. If covert recognition indexes preserved semantic information or memories about unrecognized faces and a failure of proper activation of these memories, is it possible to overcome the blocking of this activation? The present study reports several attempts at surmounting this blocking, some of which were successful in inducing the patient into experiencing a sense of familiarity with the faces of persons she knew and identifying them by name, for the first time since the onset of her illness more than 15 yrs before. This finding provides the first report of transient overt face recognition in an otherwise prosopagnosic patient.

CASE REPORT

The patient (P.V.) was a 56-yr-old right-handed French woman who contracted encephalitis of unknown aetiology in 1972. A full case description has already been published (Boudouresques *et al.*, 1979), when the patient was referred to as 'Mme V.'; only a brief summary of her condition is therefore given here. She was tested over a 3 yr period (1986–1988) and a preliminary report was made by Sergent and Poncet (1988). Only findings relevant to the questions outlined in the Introduction are reported.

Computerized tomography (CT) performed in 1975 showed a large right parietotemporal area of low density, sparing the medial posterior temporal cortex. A more recent CT scan (1985) showed the same right hemisphere damage together with a small area of low density in the left anterior temporal cortex. No significant change in her symptoms has been noticed since the start of her illness, and it is presumed that the left anterior lesion was caused by her encephalitis but was not detected in the first CT scan.

P.V. has normal intelligence (IQ of 102 on Binois-Pichot test) and no language deficit. Her Wechsler memory quotient is 87, with a lower performance on visual than verbal memory tests. Her visual fields are full and her visual acuity is 7/10. She has no deficit in colour discrimination (Munsell-Farnsworth 100 Hue Test). She has no difficulty recognizing common objects visually, and her performance on the Ghent Overlapping Figures Test is not different from that of normal controls. Her main complaints concern her complete inability to identify people by their faces, to recognize buildings and monuments, and to find her way outside her home. She also has difficulty retrieving her own belongings among objects of the same categories. This was observed with her watch and spectacles, and she was unable to identify her own handwriting among five samples.

EXPERIMENTAL INVESTIGATION

Processes underlying face perception

One of the outstanding issues in the study of prosopagnosia concerns the functional level at which the disturbance occurs, and particularly whether the deficit is primarily perceptual or mnesic in nature. While a memory impairment would leave essentially unaffected the perceptual operations, the reverse is not true, and a perceptual locus of the deficit, implying a failure to achieve configurational representations that normally underlie operations on faces (Sergent, 1989), could result in deficits on memory tasks as no reliable descriptions of the faces could be stored. Thus the same functional impairment—an inability to evoke memories associated with faces of known individuals—may result from a breakdown at different stages of face processing, and only by ascertaining the integrity of perceptual operations can the impairment be attributed to a memory deficit.

P.V. displayed no difficulty in discriminating or in matching different views of the same faces, and her performance on the Benton Face Recognition test (Benton and Van Allen, 1968) was within the normal range (46/54) and completed at a speed comparable to that of control subjects (6'21"; normals: 5'33", SD 74"). She was also able to recognize as the same person two different views of faces of French celebrities, as well as of her own face, but could not identify the individuals, including herself. Her performance on the Mooney (1960) faces was also within the range of results obtained with normal subjects in both speed (5'47"; normals: 5'12", SD 53") and accuracy, having no difficulty telling the gender (34/40; normals 36.20) and the approximate age 31/40; normals 34.78) of these fragmented faces.

In a test of immediate and delayed face-matching, she was initially presented with 20 front-view faces for 10 s each, and requested to memorize them. She was then immediately presented with these 20 faces mixed with 20 others, and asked to indicate which ones were shown earlier. Her performance was slightly above chance (14/20), but inferior to the lowest score of the normal subjects (16/20). She was then presented with the same 20 target front-view faces, but the 40 test faces were now 3/4 views, 20 of which were of the same individuals as the target faces, and the other 20 were of individuals not shown earlier. Her performance was not different from chance (12/20). About 1 h later, she was again presented with 40 front-view faces of which 20 were the same target faces and the other 20 were new faces. Her task was to indicate which faces had been shown earlier; her performance did not differ from chance (38 positive responses to the 40 faces).

The nature of the operations underlying P.V.'s perception of faces was then examined through a dissimilarity judgement task with 8 faces differing on 1, 2, or 3 features, following a procedure already used with normal subjects (Sergent, 1984) and a prosopagnosic patient (B.M., Sergent and Villemure, 1989). All 28 possible pairs of different faces were presented to P.V. and her task was to rate the degree of dissimilarity between the two faces on a scale of 1 to 9. She performed the task on 3 different occasions, and the dissimilarity judgements were subjected to multidimensional scaling (MDS) analysis. This analysis served the purpose of uncovering the rules by which the component features of the faces were combined to give rise to the percept of a face, and the data were fitted to two models that entail different combination rules. One was the city block model, which best approximates dissimilarity judgements in which stimuli are compared on the basis of their component features treated separately and additively; the other was the Euclidean model which provides the best fit of judgements based on the overall configuration of the stimuli, suggesting that the stimuli are treated in terms of their configurational properties (*see* Sergent, 1984, for a detailed description).

P.V.'s data were analysed with the program KYST-2A (Kruskal *et al.*, 1978) and were fitted to city block and Euclidean models for 2 and 3 dimensions. The goodness of fit of each solution was estimated by the 'stress' of the solution, which is a measure of how well the regression fits the dissimilarity judgements: The lower the 'stress', the better the fit. The MDS analysis showed that the three-dimensional Euclidean solution resulted in the lowest 'stress' value (0.120) followed by the two-dimensional Euclidean (0.159), while the 2 city block solutions yielded 'stress' values above 0.20. The finding of a best fit by the three-dimensional Euclidean solution is similar to results from normal subjects (Sergent, 1984) and suggests that P.V. possesses the capacity to process faces in terms of their configurational properties. This is in contrast to the finding obtained on another prosopagnosic patient (B.M.) whose dissimilarity judgements best conformed to the city block model and whose face-recognition deficit was primarily perceptual (Sergent and Villemure, 1989).

The present results suggest that P.V. has no major perceptual deficits. The cerebral damage does not invade the occipital lobes and she has no hemianopia; she can match different views of the same faces which she does not recognize and the nature of the operations underlying the perception of faces is not qualitatively different from that observed in normal subjects. Her chance performance on the delayed face-matching task and her failure to identify faces may therefore reflect a mnesic impairment in the presence of a spared capacity to achieve appropriate visual representations of faces. Her prosopagnosic disturbance must then result from operations taking place beyond the initial structural encoding (Bruce and Young, 1986; Sergent, 1989) and can be considered as a deficit at the level of stored information about faces. Whether this deficit reflects a loss of stored information or an improper activation of preserved information is examined in the next section.

Investigation of covert face recognition

Direct measures of recognition, such as delayed face-matching and face-identification, do not exhaust all memorial manifestations of personal knowledge (Richardson-Klavehn and Bjork, 1988), and this knowledge may be tapped in tasks that do not explicity call for its evocation but the performance of which nonetheless benefits from its activation. The occurrence of such benefit therefore points to the preservation and activation of at least part of this knowledge even when it cannot be explicitly evoked. This was examined by subjecting P.V. to behavioural tasks of covert recognition. Operationally, covert recognition is indexed by a change in performance as a function of the patient's familiarity with the individuals whose faces are presented in tasks that do not directly required their identification.

The individuals whose faces were used in these experiments were drawn from a pool of 120 French celebrities. At the start of the investigation, the names of these individuals were told one by one to P.V., without showing the corresponding faces, and she was asked to provide as much information as she could about these individuals. She was able to tell at least the gender, approximate age, professional occupation and two significant achievements of 64 of them. Thus P.V. still possesses memories about people which she can access from the evocation of their names. P.V. was also asked to describe the physical appearance of the faces of these 64 individuals. She could not come up with such descriptions, even about the colour and thickness of the hair and, when she attempted to describe the overall shape of the face in terms of 'round' or 'oval', she responded at random. It cannot be ascertained whether P.V.'s score reflects defective knowledge or impaired memory about famous people. The range of scores obtained on 8 age-matched control subjects was 59-108, with a mean of 92, and a score of 64 may, or may not, be low compared with what her premorbid performance would have been. In any case, faces used in subsequent tasks were drawn from the 64 individuals whose memories she could evoke on hearing their names.

Face matching. In this task, 30 pairs of faces of politicians and actors (10 women, 20 men) were used. One face of the pair was a black-and-white photograph taken in 1955, and the other face was a colour photograph of the same person taken in 1985. The age of the 'young' face varied between 25 and 40 yrs. These photographs were obtained from a French magazine and were 3.5 cm high. They were each presented on black cardboard, and no attempt was made at deleting the background as it did not provide any clue to matching. In a first part, the 60 faces were presented one after the other in a random order for identification, and P.V. failed to recognize any. In the second part, the 30 'young' faces were present in front of her, in 3 rows of 10, and her task was to place each of the 'old' faces above the corresponding 'young' faces. Both speed and accuracy served as dependent measures. While this is an easy task for subjects who know the individuals whose faces are presented, it is a difficult task for those who do not. The difficulty is due not only to the physiognomic changes resulting from the ageing process but also to the fact that these faces had different illumination and angle of view and that some of them wore a beard, moustache, or glasses in one version of the pair but not in the other. Therefore, two groups of 12 control subjects were tested, one (French subjects) familiar with the faces and the other (Canadian subjects) unfamiliar with the faces.

The results are presented in the upper part of Table 1. The two control groups performed at significantly different levels of efficiency in both speed (t (22) = 3.17, $P < 0.01$) and accuracy (t (22) = 6.84, $P < 0.001$), indicating that familiarity with the individuals greatly contributed to the performance on this matching task. P.V.'s performance was compared with that of the two control groups after transformation of raw scores into standard scores. In spite of her failure to experience any sense of familiarity with the faces, her performance was within the range of the 'familiar' group's scores ($z = 0.76$, $P > 0.20$) and significantly better than the 'unfamiliar' group ($z = 2.72$, $P < 0.01$). Thus even though P.V. was more like the 'unfamiliar' group on the test of overt recognition of the faces, she performed in a manner comparable with that of the 'familiar' group when knowledge about the faces did not have to be explicitly expressed. If familiarity benefits performance, it must be through access to stored information, and these results suggest that P.V. not only possesses implicit knowledge about the faces but can make efficient use of it in matching faces of known individuals.

An additional experiment was carried out in order to ensure that P.V.'s performance was not due to

TABLE 1. PERFORMANCE DATA ON MATCHING FACES AT DIFFERENT AGES BY THE TWO CONTROL GROUPS AND P.V.

	Controls (French) (n = 12)	*Controls (Canadians) (n = 12)*	*Patient*
Age	59	53	56
French faces*			
Faces identified	56.6	5.4	0
Matching speed	10'32" (2'06")	14'51" (2'49")	11'18"
Matching accuracy	25.2 (4.21)	14.08 (2.91)	22
Canadian faces**			
Faces identified	2.2	45.7	0
Matching speed	11'53" (2'01")	8'42" (1'38")	13'25"
Matching accuracy	8.12 (3.87)	20.92 (4.56)	5

* 30 pairs of faces were used—identification: out of 60; matching: out of 30. ** 24 pairs of faces were used—identification: out of 48; matching: out of 24.

some unusual ability to match different views of the same faces. The task was similar to the previous one, except that the faces were those of Canadian celebrities, such that 'familiarity' was reversed between the two control groups and the individuals were totally unknown to P.V. Only 24 pairs of faces of male personalities were used, and the difference in age between the two faces of each pair varied between 17 and 32 yrs. The procedure was the same as that of the previous task in all other respects.

The results are presented in the lower part of Table 1. The two control groups again differed in both speed ($P < 0.01$) and accuracy ($P < 0.001$), confirming the influence of familiarity with the faces on performance. In addition, P.V.'s performance was now comparable with that of the 'unfamiliar' group, suggesting that familiarity was the critical factor underlying her relatively high score in the previous task.

Learning task. This task was designed after the paradigm of Bruyer *et al.* (1983) and De Haan *et al.* (1987) in which a patient is asked to learn true and untrue pairings of names and faces. Covert recognition is suggested by faster learning of true than untrue pairings. Three versions of this task were conducted, using 3 different sets of 6 faces. In this, and all subsequent tasks, the faces were cut out such that no background or clothing was apparent; each appeared on a black cardboard and was approximately 5 cm high. These 18 faces were initially presented for identification by P.V., and none was recognized. In one version, faces of politicians known to P.V. before the onset of her illness were presented; the second version involved the presentation of faces of relatively newcomers on the political scene. In these two versions, the faces were associated with a family name, while in the third version, the faces were associated with a profession (actor, singer, TV presenter, politician, sportsman, businessman). In each task, 3 faces were paired with their true name or profession (e.g., Mitterrand's face with Mitterrand's name) and, for the other 3 faces, the pairing was untrue (e.g., Chirac's face with 'actor'). In each task, P.V. was initially given 2 min to learn the face-name (or face-profession) association. Then, at each trial, the 6 faces were displayed together in front of her in a random order, and each of the 6 names was called out; the task was to point to the corresponding faces. There were 10 trials in each task, and the faces were shuffled after each trial such that they appeared in a different order. Errors were corrected at the end of each trial.

The results are shown in Table 2, in terms of number of correct responses in associating a name with its assigned face at each trial for true and untrue pairings of each task. Comparisons between true and untrue pairings were conducted through a sign test (*see* De Haan *et al.*, 1987) on scores of better performance at each trial. In the three tasks, P.V. had significantly more trials in which correct responses were more frequent on true than on untrue pairings (P values < 0.01), suggesting that a correct association was established more quickly between a face and its true name than between a face and a wrong name. This was the case irrespective of whether the face was learned before or after the onset of P.V. illness, further suggesting that she has been able to acquire and store pertinent knowledge about faces in spite of her

TABLE 2. NUMBER OF CORRECT RESPONSES PER TRIAL ON THE PAIRED-ASSOCIATE LEARNING TASKS WITH TRUE AND UNTRUE PAIRINGS

	Trial no.									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Old faces*										
True pair	2	2	3	2	3	2	3	3	3	3
Untrue pair	1	0	1	3	1	1	0	0	1	2
New faces*										
True pair	0	1	3	2	2	2	3	2	3	3
Untrue pair	2	0	1	1	0	1	1	0	2	1
Professions										
True pair	1	1	2	2	3	2	3	2	3	3
Untrue pair	1	0	0	1	1	2	0	1	0	1

* 'Old' and 'new' refer to faces of politicians known before and after P.V.'s illness onset, respectively.

prosopagnosic disturbance. It cannot be determined whether these results reflect facilitation in the case of true pairings, interference in the case of untrue pairings, or a combination of these effects, but the different findings with true and untrue pairings indicate that some link could be established between faces of known individuals and their memories. However, this association between a face and its true name was not sufficient to restore a link between a face and its memories, and P.V. failed to name the faces that had been paired with their true name less than 5 min after the completion of the paired-associate learning tasks.

The present results therefore provide strong evidence of covert recognition by P.V., as indexed by perceptual and learning measures. They suggest that her knowledge of semantic information about individuals, which P.V. had no difficulty accessing through their names (as established in the initial part of the investigation), can also be at least partly, but unconsciously, accessed through their faces.

Investigation of overt face recognition

The foregoing findings indicate that, in P.V., the representations of familiar faces are linked to pertinent memories which nonetheless cannot be evoked consciously and, consequently, these faces remain meaningless. Even when P.V. succeeded in associating faces with their true names, the faces were not identified as such, and she did not express any different reaction to faces paired with their true names than to faces paired with a wrong name. In addition, the learned association between a face and its true name did not help to reestablish an efficient link between a face and its memories and P.V. failed to name such faces when presented later for identification. Yet considering that meaning lies in the particular activation of knowledge associated with a stimulus, the evidence of covert recognition suggests that some knowledge was effectively activated but was either insufficient or not specific enough to enable overt recognition. What then is the missing link between the representation of a face and the memories related to this face, and could such a link be appropriately established so as to sustain conscious overt recognition? Several attempts were made at examining the extent to which a sense of familiarity as well as overt recognition could be achieved by P.V. when various cues were provided to her.

Familiarity discrimination. P.V. was presented with 60 faces, half of which were of individuals she knew and the other half were of strangers. Each face was presented separately, and she was asked to tell whether or not it depicted a person she knew. She initially responded that she knew all the persons whose faces were presented. However, when she was informed that only half of the faces were of persons she actually knew and was again presented with the 60 faces, she responded correctly to 18 of the 'familiar' faces and to 14 of the 'unfamiliar' faces, which is not significantly different from chance. Thus the mere presentation of a face is not sufficient to trigger even a feeling of familiarity that normally precedes recognition, and this constitutes an essential component of the prosopagnosic disturbance. Her initial responses in which all the faces were rated as 'familiar' appear to be a strategy adopted by P.V. to conceal her prosopagnosia of which she is quite embarrassed. She mentioned that she usually says that she knows the faces but cannot recall the names of the persons.

Cued recognition. In this task, 48 faces, drawn from the set of 64 faces of French celebrities established earlier; were presented one after the other. For each face, a pair of names was suggested to P.V., one name being the true name and the other being one of the 48 individuals of the same gender and professional category as the individual whose face was presented. Twenty-four pairs of names were created, and each was used twice, such that each name of a pair consisted once of the true name and once of a wrong name. The task was to decide which name corresponded to the presented face. Control subjects performed this task perfectly.

Out of 48 trials, P.V. chose the correct name on 40 of them, which is significantly better than chance (χ^2 (1) = 21.34, $P < 0.001$). Her responses were made with some hesitation, but she never took more than 5 s before answering. An examination of the errors indicated that they occurred for faces whose suggested names corresponded to individuals who were of the same age and who bore a close physical resemblance to one another. Nonetheless, in 16 of the 40 faces which were correctly responded to by P.V., the 2 suggested names were those of individuals bearing the forementioned characteristics (same age and physical likeness). Only 5 pairs of names corresponded to people whose age was more than 5 yrs apart. Although this age difference may have provided P.V. with a clue to recognition, it was not sufficient to explain her overall performance. When eliminating from the analysis the 10 faces with which these 5 pairs of names were presented, P.V.'s performance (30/38) was still significantly better than chance (χ^2 (1) = 12.62, $P < 0.01$).

Although these findings indicate that P.V. was able to associate reliably a face with its name when she had to choose between two alternatives, they do not reflect a true process of recognition for at least 3 reasons. First, when initially presented with these faces, P.V. had failed to recognize any, suggesting that a face alone is not sufficient to activate all the information necessary to achieve conscious recognition. It was only through the simultaneous presentation of a face and a name that the face-name association was achieved, and this is not what a typical recognition consists of. Secondly, even though P.V. succeeded in chosing the correct name on most trials, this was not accompanied by a feeling of familiarity with the faces and she did not behave differently whether she was correct or incorrect. Thirdly, in view of these findings, P.V. was presented again with the 48 faces and a pair of names but in this task, neither name corresponded to the faces. The procedure was exactly the same as before. P.V. was first shown each face separately, without names, and she did not recognize any. When presented with 1 face and a pair of names and asked to tell the correct name, she chose 1 of the 2 suggested names as she had done earlier in all but 2 trials. The 2 exceptions were for faces of actors (Fernandel and Bourvil) which are very distinctive by their physical attributes. These two exceptions aside, she displayed no sign that she was aware that the names did not correspond to the presented faces. It thus appears that while P.V. could benefit from the simultaneous presentation of a face and its true name, her correct responses did not reflect recognition proper and were not accompanied by a feeling of familiarity with these faces.

Semantic activation. While the earlier findings indicate that an appropriate link can be established between a face and its name, they do not constitute evidence of recognition as there was no direct access from the facial representations to their pertinent memories. The next task attempted to induce recognition by narrowing the pertinent semantic information to be activated without providing any specific cue. P.V. was initially presented with 8 faces and asked to identify them, which she was unable to do. She was then told that these faces belonged to individuals sharing the same professional occupation. She spent about 10 s examining the faces, and then answered that they were politicians. Then, without any prompting, she correctly identified 7 of them, pointing to each face while telling their names. She also recognized the eighth face, mentioning that it looked familiar and providing information about his political affiliation and the ministry position he once held, but she could not retrieve his name.

The same procedure was used with 8 other faces, and P.V. was told that they belonged to the same professional category. She was again successful in finding the category (actors) on her own and proceeded in identifying each of the faces by name. When asked to comment on these faces, she could mention some particularities of the specific instances of the faces. For example, she said that 2 of the faces of comic actors (Belmondo and De Funes) had a more serious expression than they usually had, and she also noted that one of the actors (Alain Delon) looked tired and older than he usually appeared.

Two additional sets of 8 faces (singers and TV personalities) were presented to P.V. For neither of the sets was she able to find on her own the professional category to which the faces belonged, and she could not name the faces. For each set, she was then told the correct category, but this did not help her and she still was unable to express a feeling of familiarity with the faces or to recognize them. Then each name was called out and she was asked to point to the corresponding face. She pointed correctly to 1 face among the 8 singers, and to none of the TV personalities. It is noteworthy that 1 face (Yves Montand) was used both as an actor and a singer, and that P.V. could recognize him when he appeared among the 8 actors but not when he appeared among the 8 singers. Nonetheless, it was this particular face that P.V. was able to recognize when each name of the 8 singers was called out.

Finally, the 31 faces composing these 4 sets were mixed and presented one after the other for recognition. P.V. failed to recognize any, including those she had been able to name earlier.

DISCUSSION

This study was designed to assess the performance of a long-standing prosopagnosic patient on tasks involving the perception, learning, and recognition of faces, in an attempt to clarify the nature of the disturbance and to determine whether knowledge about faces could still be expressed in some covert, or even overt, form. The results showed that P.V. possessed essentially normal perceptual skills and that, despite her failure to identify faces, she could covertly access pertinent memories about individuals through the perception of their faces. In addition, P.V. displayed a transient ability to experience a true overt recognition of faces after succeeding on her own in activating appropriate semantic information corresponding to the individuals whose faces she was perceiving. These findings provide clarification of the nature of the prosopagnosic disturbance as well as new information about the fate of memories for faces in prosopagnosia.

Functional level of prosopagnosia

Whether prosopagnosia is primarily a perceptual or mnesic disturbance has been a highly debated issue. It was long held that prosopagnosia was a higher-order perceptual impairment characterized by a failure to analyse and integrate the component facial features into a meaningful percept. Faces are indeed complex multidimensional stimuli sharing the same basic conformation and characterized by small differences between one another giving them their uniqueness, such that their perception and differentiation require very fine discriminatory skills that few other categories of visual objects call for. Failure to recognize faces was thus thought to result from an impairment of these fine discriminatory skills, and the unique complexity of, and similarity between, faces among visual objects would account for the selectivity of the deficit (e.g., Lhermitte and Pillon, 1975; Levine, 1978). On the other hand, one constant finding among prosopagnosics is their poor performance in delayed-matching of faces, which could be taken as evidence of a memory involvement. However, both a perceptual and a memory locus of the deficit can explain such an outcome, either because the faces were not properly encoded at a perceptual level or because they were not reliably stored or could not be accessed at a memory level, and failure of recognition is not in itself sufficient to infer the nature of the disturbance. A dissociation between perceptual and memory performance would therefore be necessary to identify unequivocally the source of the disturbance, and Benton and Van Allen (1972) presented empirical evidence of a memory basis of prosopagnosia as simultaneous matching of faces was essentially unimpaired in some of the patients.

This divergence was clarified by Hécaen (1981) who suggested that there may in fact be two forms of prosopagnosia, one perceptual and one mnesic. Although this suggestion could, at first sight, look like an easy way out of explaining disparate findings, more recent cases of prosopagnosia seem to have confirmed Hécaen's suggestion (Levin and Peters, 1976; Bruyer *et al.*, 1983; De Haan *et al.*, 1987). The present results with P.V. offer further empirical evidence bearing on this issue, and the multidimensional scaling analysis provides a powerful technique to determine the nature of the operations by which the component features of a face are combined, and therefore to assess the integrity of perceptual processes.

The MDS analysis of P.V.'s data showed that the combination of facial features leading to the percept of a face was achieved through configurational operations by which the features were processed in an interactive manner. Such a process also characterizes how faces are perceived by normal subjects (Sergent, 1984) and constitutes an essential step in the description of facial representations and their reliable storage in cerebral structures. This suggests that P.V. possesses the capacity to encode appropriate representations at a perceptual level, and therefore that prosopagnosia may occur even in the presence of normal structural encoding of the faces. This finding contrasts with that of another prosopagnosic patient (B.M.; Sergent and Villemure, 1989) whose results from the MDS analysis indicated an inability to process faces in a configurational manner. Patient B.M. treated the component features of faces separately and independently of one another, and she was unable to achieve an integration of the features to form a configurational representation that would uniquely define each individual face. In addition, and in contrast to P.V., B.M. was unable to match different views of the same faces and also failed to display any sign of covert face recognition. The MDS analysis of the data of these 2 patients therefore provides evidence that prosopagnosia is a not single disturbance and may result from a breakdown at different levels of processing. At this point, it may be concluded that P.V. possesses essentially intact perceptual skills and is able to achieve appropriate facial representations, suggesting that the source of her prosopagnosia lies beyond the perceptual stages of processing.

Covert face recognition

The pattern of results displayed by P.V. indicates a complete inability to identify familiar persons through the mere inspection of their faces. In spite of her capacity to achieve appropriate visual representations of faces, she did not experience even a sense of familiarity with the faces which remained meaningless as a result of a failure to activate pertinent memories. Yet when memories related to the faces could be expressed indirectly, without their intentional retrieval, P.V.'s performance was significantly influenced by these memories. This was typically the case in paired-associate learning tasks in which she learned true face-name pairings faster than untrue pairings, as already observed by Bruyer *et al.* (1983) and De Haan *et al.* (1987). Even though this association could be reliably established across trials, it was short-lived and did not result in restoring an efficient link between a face and its memories, as P.V. failed to associate a face with its true name less than 5 min later. Thus whatever covert link could be established between a face and its name was not sufficient to reinstate the normal relation between perceptual and memory representations of the same individual.

This finding could indicate that the association suggested by covert recognition was not specific enough and remains at the level of familiarity rather than person identity (e.g., De Haan *et al.*, 1987; Tranel and Damasio, 1988), but the results of the other tasks in which P.V. displayed evidence of covert recognition point to a high degree of specificity in this association. Thus P.V. was able to match 'familiar' faces at different ages more efficiently than 'unfamiliar' faces, and her performance was qualitatively similar to that of the French control subjects. While 'unfamiliar' faces can only be matched on the basis of their physical appearance, the matching of 'familiar' faces benefits from the additional information that has been acquired about individuals and that both faces of the pair can conjointly access (*see* Klatzky and Forrest, 1984). Thus knowledge related to specific information about the persons depicted in the faces must have been the source of P.V.'s better performance at matching 'familiar' than 'unfamiliar' faces. However, this efficient use of pertinent and specific knowledge remains a purely automatic process over which P.V. had no control and of which she had no awareness, and it was insufficient to achieve a meaningful percept. This was clearly demonstrated in the cued recognition tasks in which P.V. successfully chose the correct name between two suggested names for a given face when one name was true and kept choosing one of the two names when neither was true. Except on two occasions, she was not aware of the mismatch between the face and the names.

It is puzzling that information about the individuals can be accessed and used appropriately without the patient being aware of having accessed this information. At least part of the pertinent information normally activated in face recognition must still be represented in prosopagnosics for covert recognition to occur, but the reason why it does not reach consciousness is still elusive. The fact that P.V. was able to achieve an appropriate representation of familiar faces that nonetheless remained meaningless to her suggests that visual representations as such do not contain information related to familiarity or identity, and their proper perceptual representation is not sufficient to sustain conscious recognition. This is consistent with models of face recognition proposed by Bruce and Young (1986) and Damasio *et al.* (1989). Therefore, conscious recognition, by which a face becomes meaningful, must be achieved by linking facial representations with knowledge or memories embedded in more anterior regions of the cortex, some of which may have been activated in the course of covert recognition.

If these anterior structures contain pertinent memories with which 'contact' could be made during covert recognition, what then prevented their full activation for overt recognition? Even if memories related to faces, normally embodied in temporal cortices, were disturbed, this is insufficient to explain P.V.'s prosopagnosia. These memories are not lost since they can be accessed by calling the name of the individuals, and all the faces used in these tasks were of people known by P.V. It is also the case that P.V. was still able to acquire knowledge about 'new' faces, as indicated by her covert recognition of faces to which she was exposed only after the onset of her illness, which implies preserved functioning of hippocampal structures and absence of anterograde amnesia for faces (Rolls, 1989). In addition, P.V.'s capacity to recognize faces overtly under some conditions also indicates that pertinent memories were accessible. All this suggests that neither the facial representations nor the semantic information were critically disturbed in P.V., and her prosopagnosia may thus reflect faulty connections between faces and their memories, perhaps characterized by a heightened threshold of activation of the information that underlies conscious recognition. Such a heightened threshold may result from a reduction in the effectiveness of synaptic transmission, as evidenced by slow processing time observed in prosopagnosics (e.g., De Haan *et al.*, 1987), or from a form of reduced arousal which also has been noted in some prosopagnosics (e.g., Bauer, 1984; Habib, 1986). Because faces, as opposed to visual objects, come in many exemplars which must all have their unique memories for recognition as individuals, the proper evocation of relevant memories may require the reactivation of a large amount of information necessary to differentiate each face, and this activation may not go all the way, or may be blocked before the final stages from which conscious recognition would emerge.

The evidence that P.V. is capable of covert recognition of faces she does not overtly recognize indicates that this phenomenon does not depend on the duration of the illness. Given the long-standing prosopagnosia of P.V. (since 1972), the fact that covert recognition had so far been observed only in patients whose illness had lasted less than 10 yrs was of no significance. One condition for the occurrence of covert recognition may then be the integrity of perceptual skills that allow the patient to extract the physiognomic invariants that uniquely describe a face so as to achieve a reliable discrimination among faces necessary to activate pertinent stored information. If such skills are impaired, the particularities of the features and of their arrangement that make a face unique can no longer be extracted and recorded, and facial representation lose their specificity. The absence of covert recognition in patients whose disturbance is primarily perceptual (Bauer, 1986; Newcombe *et al.*, 1989; Sergent and Villemure, 1989) may thus result from the inability to build up faithful facial representations rather than to a memory deficit per se.

Overt face recognition

Another important finding of this study is the first demonstration of overt recognition by a prosopagnosic in the absence of specific cues from the experimenter. This was achieved after P.V. succeeded in inferring the professional category of the faces she was presented with, and it was indicated by her capacity to name, or to provide semantic information about, the individuals whose faces were presented. This successful naming of faces did not occur by chance, and P.V. was quite aware that these faces were familiar to her and that she knew them. In so far as retrieving the name of a face constitutes an end-product of prior processing of semantic information related to this face (Bruce and Young, 1986), P.V.'s correct naming of the faces indicates that she had efficiently accessed and processed the relevant semantic information. Although prior exposure to the faces during the various tasks may have contributed to their recognition, it is not sufficient to explain P.V.'s performance. Not all faces of politicians and actors of the initial set of 64 faces were used in this task, yet she made no confusion and the correct naming of 7 out of 8 politicians and of 8 out of 8 actors cannot have occurred by chance.

It remains unexplained why P.V. was successful with 2 sets of 8 faces but not with the other 2 sets, but this outcome may help highlight some of the conditions that may have underlied the occurrence of overt face recognition. One was the capacity to access some pertinent memories related to these faces, and it was only after these memories had been activated that P.V. recognized the faces. A second condition was that this activation be achieved by the patient herself. When P.V. failed to find the appropriate category on her own and was told the name of that category, this did not result in recognition. Thus her failure to recognize singers and TV personalities, even when told the category and when each name was called out, indicates that the activation of pertinent semantic information from the facial representations was required for a true process of recognition to occur. The mere mention of the category by the experimenter was not sufficient to promote recognition.

A third condition may be suggested by the fact that the evocation of pertinent memories, which could not be overtly achieved from the presentation of a single face, was now possible when a large array of faces was related to the same categorical semantic information. Several factors may have contributed to this overt evocation of categorical information. First, because information is categorically organized in the brain (Warrington and Shallice, 1984; Damasio, 1990), as a result of the frequent co-occurrence of exemplars of the same category, presenting several faces belonging to the same category may enhance the probability of activating this semantic categorical information, as connections from each face may converge on closely related memories linked by their sharing the same category. In this sense, the simultaneous presentation of instances of the same category may have raised the activation level above the heightened threshold and established the appropriate link between faces and part of their memories. Secondly, the fact that the mere mention of the name of the category was unsuccessful at promoting recognition may suggest that it was not the concept of 'politician' or 'singer' that was the critical factor. Instead, the presentations of several faces resulted in the activation of unique memories of persons which all belonged to the same category, and it was this conjunction of activation, as opposed to activation from a single face, that may have overcome the blocking characteristic of P.V.'s prosopagnosia.

It may be tempting to speculate, from P.V.'s transient ability to recognize faces overtly, that her performance reflected, in slow motion and stepwise manner, the normal unfolding of face-recognition processes. Thus the foregoing considerations suggest that it was through a series of interactions between the representations of faces and their memories that recognition could be achieved, first by activating the semantic knowledge related to the present faces, then by a feedback from this knowledge to the facial representations which acquire a sense of familiarity. Further activation of information about the individuals could be achieved through additional interactions between specific pertinent memories and faces which then became meaningful and were overtly recognized. Such a series of activations and retroactivations between different levels of representations of information, making use of forward and backward projections multiply linking cortical areas, may underlie the processes of visual recognition, as has been hypothesized by Damasio *et al.* (1989) and Rolls (1989). While feedforward projections are a typical feature of models of cerebral processing and object recognition, the role of backward projections, which are so pervasive in the visual cortex (e.g., Jones and Peters, 1984), are not usually included in such models. Yet these projections may be necessary for a percept to achieve its meaning. If the neural pattern of activity underlying the perception of a face takes place in posterior retinotopically organized structures, and because such a percept is meaningless until it evokes pertinent memories, the activation of these memories must be signalled back to posterior structures for the perceived face to become meaningful. That such backward projections are critical for recognition and were not operating properly in P.V. is further suggested by her failure to 'image', and provide a description of, the faces of people she knew. Whereas she could access semantic information about these people from the evocation of their names, this semantic information failed to activate the appropriate facial representations, even though the structures underlying these visual representations were still functional.

The occurrence of overt recognition in P.V., together with her essentially unimpaired perceptual skills, seem to indicate that her disturbance is neither primarily mnesic nor primarily perceptual. Instead, it affects the processes of visual recognition of objects that are defined by unique memories which can no longer be activated properly by their perceptual representations. This form of prosopagnosia, by contrast with a perceptually-based deficit in which the encoding of physical attributes is impaired, may be susceptible to be overcome to some extent, as some of the processes underlying normal recognition are still taking place but fail to promote overt recognition in most circumstances. Further attempts at inducing overt recognition would be necessary to uncover its underlying structures and mechanisms and to determine whether P.V. is unique in her capacity momentarily to escape her prosopagnosia.

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HEMISPATIAL NEGLECT IN A PATIENT WITH CALLOSAL INFARCTION

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SUMMARY

Left hemispatial neglect, confined to right-hand and verbal responses, was exhibited by a 56-yr-old right-handed male patient with callosal lesions due to cerebral infarction. Various disconnection signs were also present. His CT and MRI scans disclosed major lesions situated in the posterior half of the genu and the whole trunk of the corpus callosum, as well as in the left medial frontal and temporo-occipital lobes. Left hemispatial neglect was invariably demonstrated in right-hand performance such as copying drawings, line bisection, matching identical figures and copying multiple digit numbers, and in verbal performance such as confrontation naming and reading aloud multiple digit numbers. In contrast, little or no right hemispatial neglect was demonstrated in tasks performed with the left hand. These findings support the hypothesis that the left hemisphere is only concerned with attending to the contralateral hemispace and that the right hemisphere is specialized for attending to both sides of space although the preponderant tendency is for attending to the contralateral hemispace. The neglect symptoms observed in our patient may be a disconnection sign which was attributable to a combination of lesions in the corpus callosum and in the left medial frontal lobe.

INTRODUCTION

It is generally accepted that hemispatial neglect is manifested in the contralateral hemispace of a damaged hemisphere, and that right hemisphere lesions cause more frequent and more severe neglect than those in the left hemisphere (Costa *et al.*, 1969; De Renzi *et al.*, 1970; Gainotti *et al.*, 1972; Albert, 1973; for reviews, *see* Heilman *et al.*, 1985, and Mesulam, 1985). It is plausible to argue that theoretical considerations on hemispatial neglect must be based on such asymmetric manifestations of hemispatial neglect (Friedland and Weinstein, 1977). A few cogent hypotheses have been put forward to explain this asymmetry.

Kinsbourne (1977) argued that each hemisphere explored contralateral hemispace although the exploration of the left hemisphere into right hemispace was more powerful than that of the right hemisphere into left hemispace. He also pointed out that right- and left-orientating tendencies were in a reciprocal system; if one hemisphere was

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inactivated, the other was disinhibited. Based on these mechanisms, a right hemisphere lesion released the function of the left hemisphere resulting in left hemispatial neglect. He further argued that activation of the left hemisphere by linguistic activities enhanced exploration into right hemispace, resulting in the more frequent occurrence of left hemispatial neglect in patients with right hemisphere lesions.

On the other hand, models based on the asymmetry of attentional direction of the two hemispheres have been proposed. Following the suggestion by Heilman and Valenstein (1979) that the right hemisphere dominated the attentional processes, Heilman and Van Den Abell (1980), on the basis of electroencephalographic data of normal subjects, proposed that the right hemisphere attended to stimuli presented to both the right and left sides while the left hemisphere could not attend to ipsilateral stimuli. Heilman *et al.* (1985), in explaining a mechanism of hemispatial akinesia, argued that the right hemisphere could prepare the limbs physiologically to work in (or towards) either right or left hemispace, but that the left hemisphere could only activate them to work in (or towards) right hemispace. In a review article, Mesulam (1981) expressed a similar view but limited the ipsilateral attentional capacity of the right hemisphere to a lesser extent than the contralateral one. He postulated that (1) the intact right hemisphere may contain the neural apparatus for attending to both sides of space, although the predominant tendency was for attending to the contralateral (left) hemispace; (2) the left hemisphere is almost exclusively concerned with attending to the contralateral right hemispace; and (3) more synaptic space was devoted to attentional functions in the right hemisphere than in the left, so that most attentional tasks involving either hemispace would generate greater activity in the right hemisphere. Weintraub and Mesulam (1987) supported this model with their experimental data, where patients with right-hemisphere damage showed neglect in ipsilateral hemispace, although not as severe as in contralateral hemispace. These asymmetric attention models, including that of Kinsbourne, seem capable of explaining differences in the spatial lateralization and severity of neglect resulting from damage to the right or left hemispheres.

If directed attention is asymmetrically represented in the right and left hemispheres, it would be anticipated that patients with callosal lesions might demonstrate unimanual hemispatial neglect because an inferior hemisphere is obliged to run by itself, as in the case of the linguistically nondominant hemisphere yielding unimanual agraphia, tactile anomia and so forth in callosal disconnection. However, as far as commissurotomy patients are concerned, salient neglect has not been described (Sperry *et al.*, 1969; Gordon *et al.*, 1971; Joynt, 1977; Plourde and Sperry, 1984; Bogen, 1985), although neglect only in the acute period (Wilson *et al.*, 1977), rudimentary neglect in the chronic period (Plourde and Sperry, 1984) and the superiority of the right hemisphere in attentional capacity (Dimond, 1976) have been reported. Thus the absence of salient neglect in commissurotomized patients has been a serious obstacle in the acceptance of the hemisphere asymmetry models of directed attention.

What interpretation has been given to the lack of prominent neglect in commissurotomy patients? Holtzman *et al.* (1981) proposed that each hemisphere is provided with bilateral visual representation for the allocation of attentional resources. Plourde and Sperry (1984) also suggested that each hemisphere has the capacity for exploration and representation of both sides of space, although the right hemisphere has the lead role in cognitive operations that involve spatial relationships as well as for certain attentional tasks. These authors considered that the left-sided awareness of the left hemisphere was subject to differential suppression in the presence of the cerebral commissures via disruptive influences from a focally damaged right hemisphere. Heilman *et al.* (1984), on the basis of the data from a patient with callosal damage due to infarction, suggested mechanisms which presupposed that each hemisphere attended only to contralateral hemispace independent of the sensory field or extremity used. In conclusion, the observations on commissurotomy patients seem to support symmetric cerebral representations of directed attention whether each hemisphere is postulated to orient unilaterally or bilaterally.

More recently, however, hemispatial neglect has been sporadically described in patients with callosal lesions due to cerebrovascular disease. Sine *et al.* (1984) observed a right-handed patient with a cerebral haemorrhage, who showed a callosal syndrome and left-sided neglect confined to the right hand when drawing a clock. The CT scan demonstrated a haemorrhage in the left parasagittal frontoparietal area and an angiogram on day 4 demonstrated spasm of the A-1 segment of the anterior cerebral artery. Furthermore, a right-handed patient of Goldenberg (1986) with destruction of the anterior two-thirds of the corpus callosum and the adjacent medial frontal lobes as a sequel of bleeding from an anterior cerebral artery aneurysm, displayed neglect of left hemispace limited to her right hand. To date, these case studies have never come to adequate attention in the literature. The present authors had the opportunity to examine a patient with callosal lesions due to cerebral infarction who demonstrated signs of unilateral hemispatial neglect not only confined to the right hand in visuomanual tasks but also in verbal responses for visuoverbal tasks. Observations supporting the hemisphere asymmetry models of directed attention advanced by Heilman and Van Den Abell (1980) and Mesulam (1981) have been reported. On the basis of these hemisphere asymmetry models, we will further explore the possibility that the asymmetric neglect observed in our patient may be a disconnection sign and that medial frontal lesions may in addition contribute to callosal lesions.

CASE REPORT

Y.Y. was a 56-yr-old government official with 16 yrs of education, completely right-handed according to our handedness enquiry list consisting of 14 questions about manual dexterity. He had no left-hand genetic relatives. He developed sudden paresis of the right lower limb in December 1983 and was admitted to a local hospital. He was diagnosed as having had a cerebral thrombosis, but no lesion was detected on a CT scan. He began work again in September 1984 but needed assistance both in commuting and in office work. On July 14, 1985, he was found unconscious in bed by a family member and brought to another local hospital. His CT scan disclosed a large low density area extending from the temporal to the occipital lobes in the left hemisphere. He was transferred to Kyoritsu Rehabilitation Hospital for further investigation and rehabilitation on October 31, 1985.

Y.Y. was alert and cooperative in examinations, although his face was somewhat expressionless. He was disorientated in time and space because of amnesia, but his general intelligence was not grossly impaired. A right homonymous hemianopia was demonstrated on confrontation. The other cranial nerves were normal.

Tendon reflexes in both lower limbs were moderately exaggerated but there was no right-left difference. Pathological reflexes and ankle clonus were absent. Muscle tone was normal. He was not ataxic. Although showing neither gross paresis nor definite sensory loss, he demonstrated a small stepped 'arteriosclerotic'

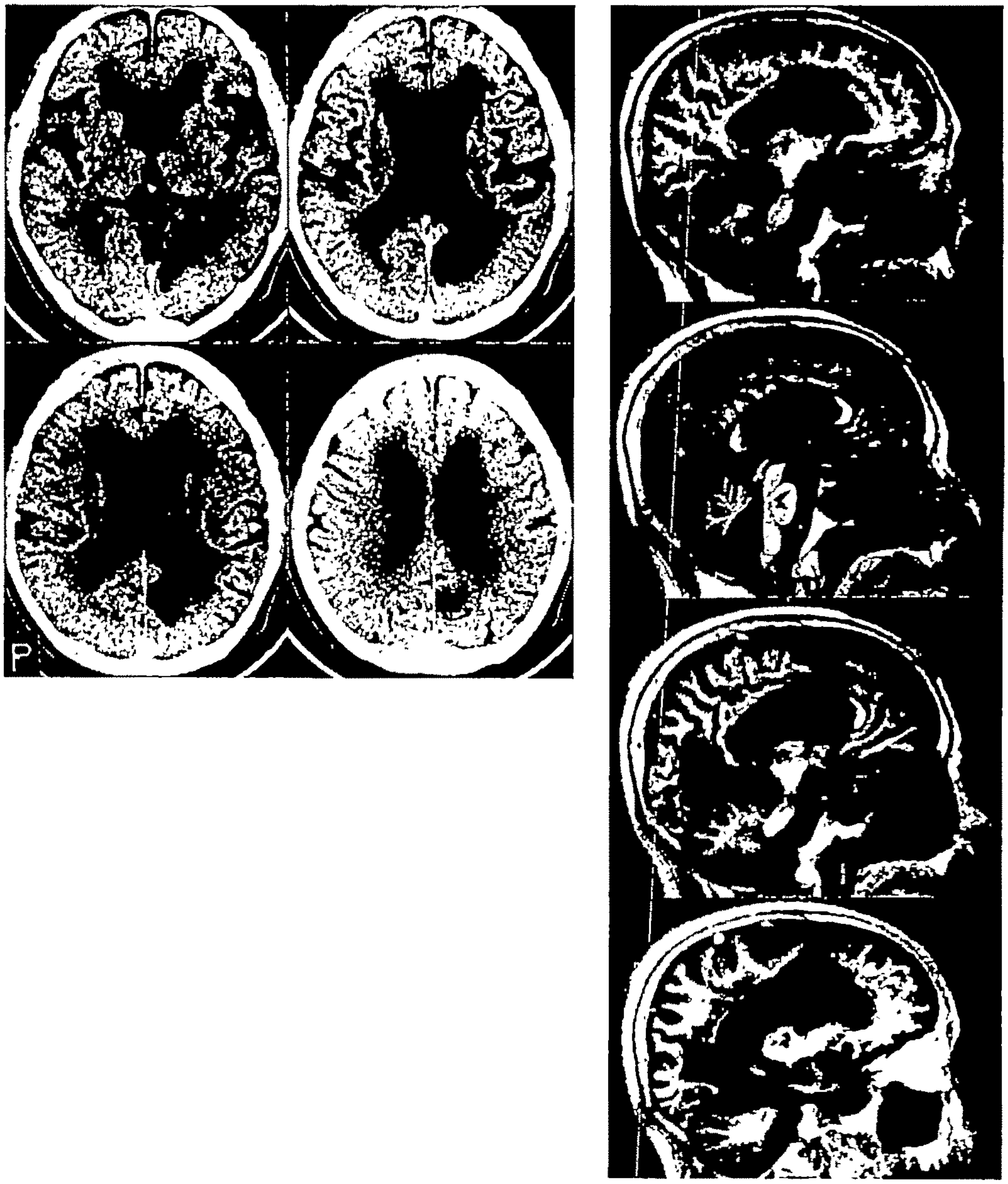


FIG. 1. *Left*: CT scans (December 3, 1985), *Right*: MRI sagittal planes (February 20, 1986). IR method: TR = 2100 ms, TI = 600 ms, from the top, 1.2 cm to the right of the median plane, the median plane, 1.2 cm to the left, and 2.4 cm to the left.

gait (démarche à petit pas) with a freezing phenomenon in the right leg and desynchronization in manual pronation-supination diadochokinesis. No grasping reflexes were demonstrable.

The CT (December 3, 1985) and MRI scans (February 20, 1986) showed lesions situated in the posterior half of the genu, the whole trunk of the corpus callosum, the posterosuperior portion of the left medial frontal lobe, and in the left medial temporo-occipital lobes (fig. 1). Spots of low density were also found in the basal ganglia bilaterally, the thalamus and the pons.

Neuropsychologically, Y.Y. showed marked ideomotor apraxia, agraphia, and tactile anomia confined to the left hand. Apraxia was conspicuous in response to oral commands resulting in perseveration, but improved slightly on imitation. He could manipulate objects without difficulty. His agraphia did not improve with the use of anagram kanji and kana. Diagonistic apraxia was also observed. For example, the left hand tried to grasp a pencil held with the right hand with which he intended to write. He exhibited neither auditory extinction to nonverbal or verbal stimuli, nor tactile extinction when manual responses were required. However, when verbal responses were required, auditory or tactile stimuli to the left ear or hand were almost completely extinguished in bilateral simultaneous stimulation tests. The details of these phenomena, designated as 'apparent extinction', were reported by Nishikawa *et al.* (1988). Visuomotor ataxia (ataxie optique) was present with the right hand in the left visual hemifield. Only the left hand demonstrated marked difficulties in forming rhythmic patterns. Details of this symptom have been reported previously (Kashiwagi *et al.*, 1989). These findings led us believe that he had a callosal disconnection syndrome. He was not aphasic from the beginning of our observation, but we are uncertain whether he had been at an earlier stage. According to the WAIS, his verbal IQ was 63 and his performance IQ was off scale with either hand. His verbal IQ was poorer than expected, but he could cope with an intellectual conversation when he was spoken to.

INVESTIGATIONS ON HEMISPATIAL NEGLECT

On admission (November 1985), we observed that Y.Y. showed left hemispatial neglect in line cancellation, copying sentences, spontaneous writing when performed with the right hand, and in reading sentences aloud. When asked to copy line drawings, his right hand demonstrated hemispatial neglect on the left side of the drawings, and constructional disturbances and perseveration in the right half of the copied drawings. His left hand seemed to display no neglect although the details were not clearly drawn.

His left hand showed conspicuous agraphia, producing completely unintelligible scrawls in spontaneous writing. His performance in copying characters with the same hand was slightly better. Later (September 1986), his left hand improved for copying characters to such a degree that we could conduct further studies. The following investigations were conducted from September 1986 to December 1987. He had no further attacks or changes in his general condition or neuropsychological state from the time of admission to the end of 1987.

Copying line drawings: complete figures (November 1986)

Methods

Y.Y. was asked to sit in front of a desk so that the line of his shoulders was parallel to the front edge of the desk. He was then asked to copy black line drawings (5×5 cm). Model drawings had been made on the upper half of a sheet of white paper (18×13 cm) and he was to draw under the model on the same sheet. The drawings employed for models were a crab and a butterfly (*see* fig. 2). The stimulus sheet was placed on the desk in three different spatial positions, i.e., centrally, right hemispace and left hemispace (as suggested by Heilman *et al.*, 1984). In the central space, the stimulus sheet was aligned with the midline of the patient's body. In the right hemispace, it was placed on the desk so that the midline of the sheet was aligned at 45° to his body. In the left hemispace, it was placed in a corresponding position to the left. A total of 6 trials (2 drawings ×3 spatial positions) was performed with each hand.

Results

As fig. 2 shows, the fundamental characteristics of the copied drawings did not vary with drawing or spatial position. The left hand showed no neglect, whereas the right displayed almost complete neglect on the left side. Constructional disturbances and perseveration were also discernible in the copies made with the right hand. The patient spoke very little while copying and made no reference to the neglected part of his own copies. He once wrote explanatory words alongside what he had drawn (fig. 2). He often exhibited signs of irritation, saying that he had not been able to copy well as he had been poor at drawing before his illness. When asked how well his copies had been executed, he commented 'They were done badly'. His wife said that he had not been good at drawing.

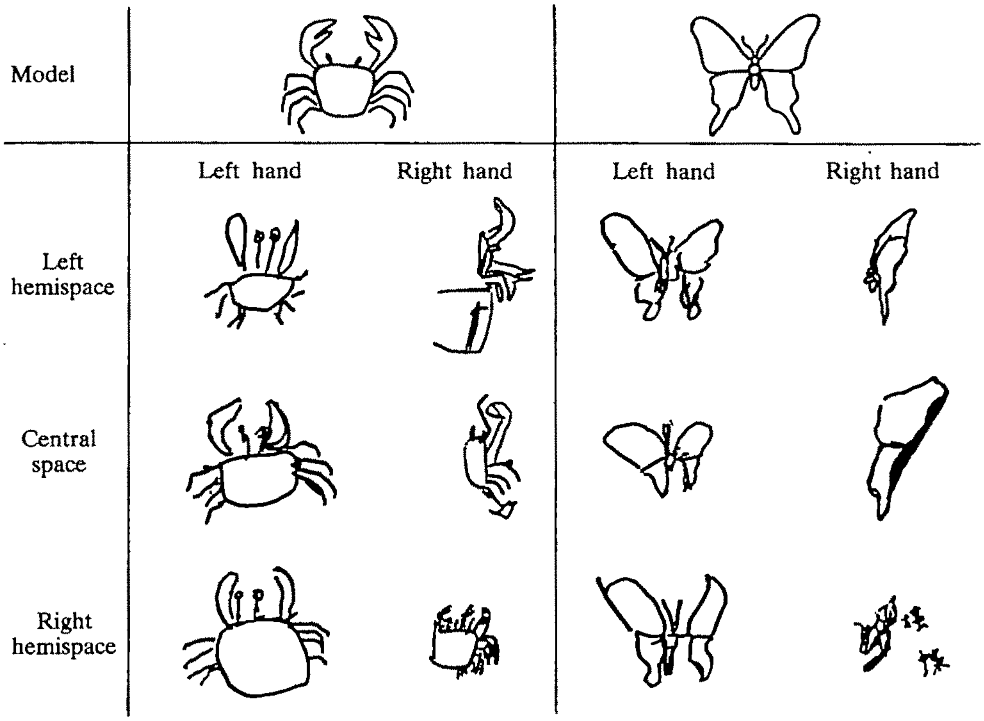


FIG. 2. All the responses in copying complete figures, edited for demonstration. The Chinese characters (kanji) read as 'choucho' (a butterfly) were written by the patient alongside one of his copies (right hemispace: right hand).

Copying line drawings: half figures (August 1987)

In order to determine whether the attention of the left hemisphere was restricted to the right half of figures under a different experimental condition, a task that involved copying half figures was administered.

Methods

Half figures were made by bisecting the same drawings as had been employed for copying complete figures. The patient was asked to copy them with each hand. A test sheet was presented only in the central space. The rest of the test procedure was the same as for the copying of complete figures.

Results

As displayed in fig. 3, almost the same results as for the copying of complete figures were obtained. It was noted that the right hand tended to copy only the right side of the left half models. No evidence was obtained that a half model was copied as a complete figure (Gazzaniga and Smylie, 1984).

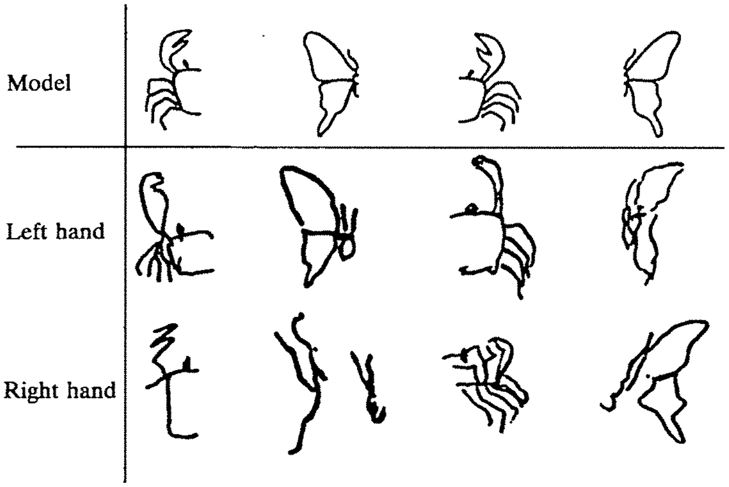


FIG. 3. All responses in copying half figures, arranged for display. The smaller drawing of the left half butterfly was drawn for the second time following an instruction to copy again.

Line bisection (September 1986)

Methods

Seated at a desk, the patient was asked to bisect a visually presented, horizontally orientated line drawn in black ink, with each hand using a pencil. The line was 2 mm wide and was placed in the middle of a 12×36 cm sheet of white paper. Five different line lengths (16, 20, 24, 28 and 32 cm) were used. As in the test of copying complete figures, a stimulus sheet was placed on a desk in 3 different spatial positions: central space, right hemispace, and left hemispace. A session comprised 6 blocks, that is, all combinations of hands and spatial positions. Both the blocks in a session and the 5 lines in each block were randomized. The distance between the estimated and actual midpoints was measured to the nearest millimetre and was expressed as a rate of deviation or a percentage of the half length of a corresponding line. Deviations to the left of the actual midpoint were assigned a negative value. The session was repeated 2 days later.

Results and Discussion

In fig. 4, the black triangles indicate the point that the patient considered to be the midpoint of the line. Mean rates of deviation for two sessions are inserted block by block with a vertical dotted line.

An analysis of variance (ANOVA) for repeated measures was performed on these data with hand (right, left), spatial position (central space, right hemispace, left hemispace), and length of lines (5 lengths) as factors. The results of this analysis revealed that hand and spatial position were significant (F(1, 30) = 66.85, $P < 0.01$; F(2, 30) = 17.02, $P < 0.01$, respectively). The length of the lines and all the interactions were not significant.

Based on the line bisection task (16 cm, in the central space) conducted for right-handed normals, Imamura *et al.* (1988) determined the normal range of deviation as less than 9.6% rightward and 8.3% leftward,

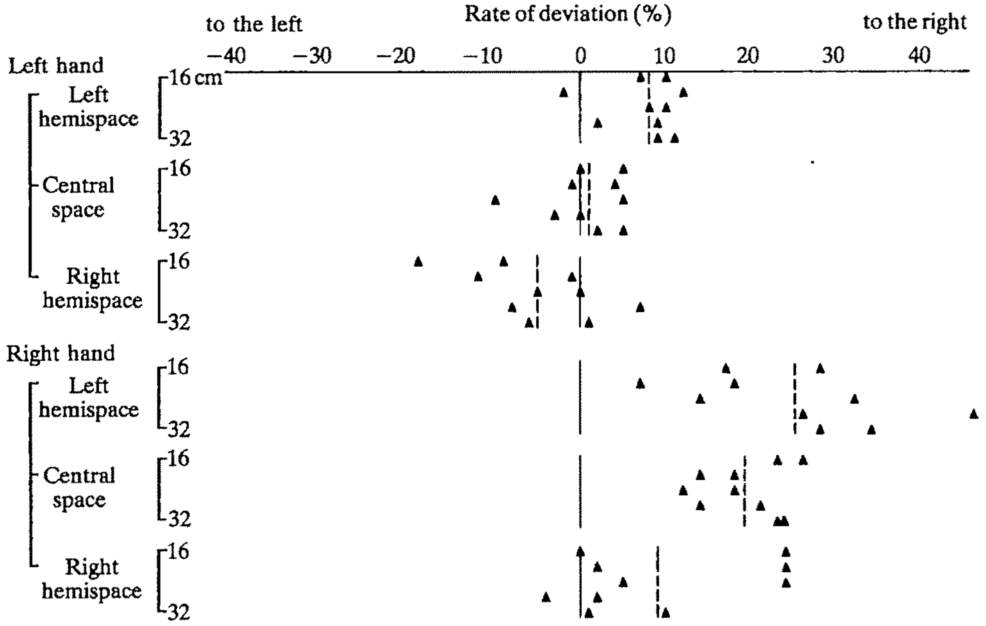


FIG. 4. Deviation rates of line bisection. For each block, deviation rates (%) were calculated in terms of dividing a deviated length by a half length of a line and plotted with black triangles. Dotted lines represent the means, calculated block by block.

regardless of the hand used. Taking these data into consideration, the performance of Y.Y.'s left hand in central space was considered to be normal. Both the rightward deviation in left hemispace and the leftward deviation in right hemispace were slight. On the other hand, performance with the right hand revealed marked deviations towards the right in left hemispace and central space, while deviation was less conspicuous in right hemispace with the right hand. This dissociation between hands could be explained by the weak attentional capacity of the left hemisphere in ipsilateral hemispace.

Heilman *et al.* (1984) summarized the line bisection data of a patient who had a partial callosal disconnection due to cerebral haemorrhage as follows. Each hand appeared to deviate towards its own hemispace and this was most apparent when the hand was required to operate in the contralateral hemispace. The overall tendencies of right-hand performance were similar to the results for Y.Y., whereas those of the left-hand performance differed. It is difficult to determine the relationship between the neglect signs shown by Y.Y. and what Heilman *et al.* designated as 'pseudoneglect'.

Confrontation naming (August 1987)

Difficulties in naming due to hemispatial neglect were examined with respect to directional attention of the left hemisphere.

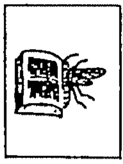
Methods

Twenty familiar drawings, which were symmetric about their vertical midline and easily recognizable, were selected. Some of them were taken from Sasanuma's drawing cards (Sasanuma *et al.*, 1978). Each had four different variants as illustrated in fig. 5. One of the variants was designated as a complete figure, i.e., an original drawing. The second variant was designated as a chimeric figure: 20 right half figures were paired with a left half figure arbitrarily selected. The third variant was a right half figure, which

Complete figure

Correct	80.0%
Incorrect related	20.0
Total	100.0

Chimeric figure

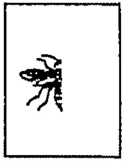


	Responses to the right halves			
	Correct	Incorrect		Total
		Related	Don't know	
Responses to the left halves				
Correct	0.0%	0.0	0.0	0.0
Incorrect				
Referred to the left halves				
Unrelated	5.0	2.5	0.0	7.5
Perseverated	5.0	2.5	0.0	7.5
Not referring to the left halves	75.0	5.0	0.0	80.0
Unclassified	0.0	0.0	5.0	5.0
Total	85.0	10.0	5.0	100.0

Right half figure

Correct	85.0%
Incorrect related	15.0
Total	100.0

Left half figure



Correct	42.5%
Incorrect	
Related	10.0
Related or perseverated	5.0
Unrelated	5.0
Perseverated	20.0
Don't know	17.5
Total	100.0

FIG. 5. Confrontation naming. Mean percentages correct of each type of response for the total of the two sessions are shown in the tables, and examples of the 4 variations of figure cards are illustrated.

was made by erasing the left half of an original drawing. The final variant was a left half figure, which was made by erasing the right half. All of these figures were drawn in black ink without a line frame, so that the midline of symmetry coincided with the midline of a 9×6 cm card. The cards were presented on the desk one by one so that the midline of the card coincided with the midline of the patient's body. The patient was instructed to name a drawing presented in free vision and to say what he noticed about the drawing. No restriction in response time was imposed. A total of 80 figures were presented randomly. The test was repeated 2 days later, using the same procedure.

Responses for each figure type were classified into the categories listed in fig. 5. Responses which named either a morphological or semantic relationship to a stimulus drawing were classified as 'related'.

Results and Discussion

The results of the 2 tests were almost equal. The mean rates for both were subjected to analysis. The results are listed for each type of response in fig. 5 and summarized as follows. (1) For complete figures, there were 20% incorrect responses, all of which were 'related'. (2) For the chimeric figures, 85% of the right halves were correctly named but, in contrast, none of the left halves was named correctly and 80% were not even referred to. (3) Right half figures tended to be correctly named (85%). (4) The left half figures were named correctly less than half as often as the other types of figures (42.5%). Among incorrect responses, perseveration and 'don't know' responses predominated (20% and 17.5%, respectively).

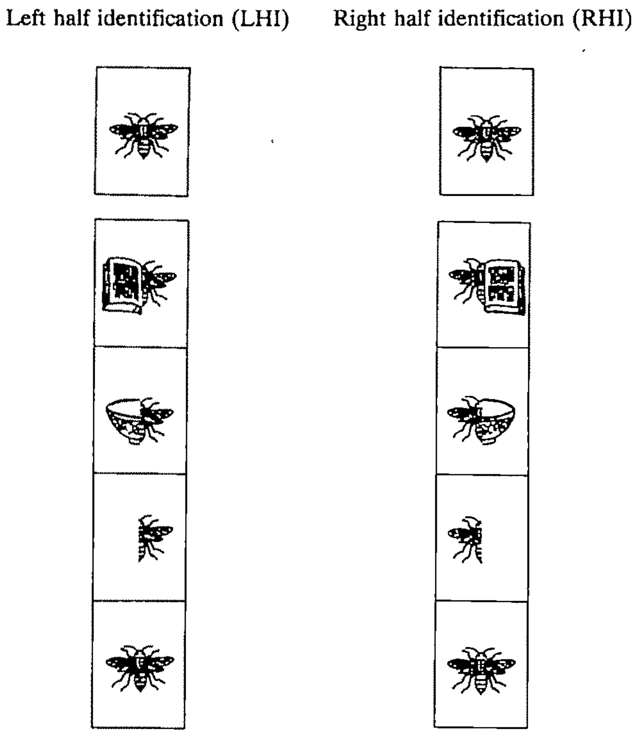
We interpreted these results as follows. (1) In chimeric figures, Y.Y.'s left hemisphere attended strongly to the right half of a figure but weakly to the left half. High scores were obtained only in response to the information from the right half. (2) In naming right half figures, good scores were obtained. According to the earlier results of copying right half figures with his right hand, Y.Y. attended predominantly to the right half of a right half figure. It can be surmised that when the left hemisphere was ready for confrontation naming, the rightward field of attention for right half figures was narrower than that for chimeric figures. Nevertheless, the scores of right half figures and the right half of chimeric figures were the same. He could presumably command enough information for naming from the right half of right half figures, given the symmetric nature of the object whose distinctive visual features were lateralized to the periphery. (3) In naming left half figures, we presume that Y.Y. attended only to the right side of left half figures. As a result, he was presumably seeing an unfamiliar figure, and this lack of visual information resulted in the poorest scores for all the tasks. Note also that the left half figures were drawn on the left side of the midline of the card in an area to which the left hemisphere was supposed to be poor. Thus the two factors resulting in a paucity of attention to the left side might be responsible for his poor performance in this task. (4) In naming complete figures, Y.Y. produced almost the same number of incorrect responses as in naming chimeric or right half figures. It is supposed that the same amount of decrease in information, or the neglect of the left side, might affect the naming processes. All the incorrect responses were morphologically and semantically related, that is, when enough information for naming was not available from the part to which he attended, he misnamed it. (5) All of these phenomena suggested that Y.Y. had a naming deficit due to left hemispatial neglect. The left hemisphere probably had a reduced attention capacity directed to ipsilateral hemispace.

Matching identical figures (December 1987)

To examine further the characteristics of hemispatial neglect in the visual processes where the influence from kinetic bias was minimized, a task involving the matching of identical figures was performed. Discriminative information was placed in only one half of the figure: left half identification (LHI) and right half identification (RHI).

Methods

Y.Y. was asked to point, with each hand, to the figure identical to a stimulus figure among 4 choices on a multiple-choice board. A multiple-choice board was placed on the desk in front of him and on the



Left half identification (LHI)

Right half identification (RHI)

FIG. 6. Examples of a stimulus and multiple-choice board for left half identification (LHI) and right half identification (RHI) in matching identical figures.

top of it was placed a stimulus board. In LHI, as shown in fig. 6, the right halves of the 4 figures on a multiple-choice board were all identical with the right half of a stimulus figure so that distinctive information for the identification was lateralized to the left halves of the figures. Figures for RHI were prepared so as to be symmetrical to LHI figures. The remaining conditions were identical.

Five symmetric and easily recognizable drawings (9×6 cm) of common objects (a bee, a hat, a bell, a tree, and Chinese noodles in a bowl) were prepared. For the LHI task, 3 kinds of stimulus figures and 3 kinds of multiple-choice boards per drawing were prepared. A right half figure, a chimeric figure (a right half figure attached to the left half figure of a different drawing), and a complete figure (an original drawing) were employed for stimulus figures. The multiple-choice board contained 4 choices: the 3 figures as were used for a stimulus, plus 1 additional chimeric figure. These 4 choices were aligned vertically to avoid horizontal bias due to directional neglect and were distributed in each position once through the 3 boards so that distributional bias could be avoided. The 3 multiple-choice boards were paired randomly with 1 of the 3 stimulus boards for matching. Thus 15 sets (3 stimulus boards ×5 drawings) were prepared. Completely identical sets were prepared for the RHI task.

The vertical midlines of the stimulus board and the multiple-choice board were always set on the desk coinciding with Y.Y.'s midline to minimize the influence of lateral movements in visual searching and pointing with hands.

The 30 trials (15 sets each of LHI and RHI) were randomized and performed with randomly ordered right-hand and left-hand pointing. Response time was measured. The test was repeated 3, 6 and 9 days later.

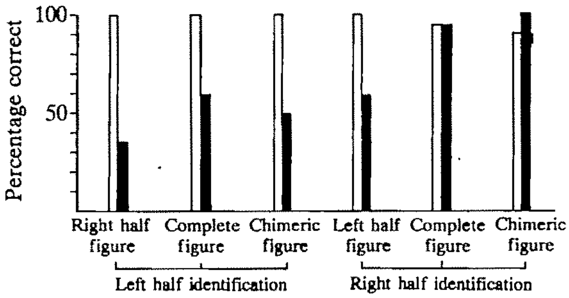


FIG. 7. Matching identical figures. Mean percentages for the total of correct responses in the four sessions. Open column = left hand; closed column = right hand.

Results and Discussion

Since Y.Y. correctly performed almost all trials within 5 s with his left hand, we gave 1 point for a correct response produced within 5 s. Otherwise, no point was given. The mean scores of the four sessions are charted in fig. 7. ANOVA for repeated measures was performed on these data by hand (right, left), type of identification (LHI, RHI), stimulus figure (half, complete, chimera), and drawing (5 objects) as factors. The results were as follows. (1) Hand, type of identification, and the interaction between these 2 factors were significant (F(1, 3) = 21.07, $P < 0.05$), (F(1, 182) = 15.44, $P < 0.01$) and (F(1, 182) = 26.74, $P < 0.01$), respectively. (2) The stimulus figure was also significant (F(2, 182) = 4.41, $P < 0.05$). (3) An interaction between hand and stimulus figure was significant (F(2, 182) = 7.23, $P < 0.01$). (4) The drawing was not significant. (5) The other interactions were not significant. Tukey's multiple comparisons among the percentages correct for the 6 conditions revealed the following. (6) The left hand responded moderately well under all of the 6 conditions (3 stimulus figures ×2 identification types) and showed no significant differences among them. (7) The right hand responded well to the complete and chimeric figures in RHI. There was no significant difference between them. However, if compared with the performances under these two conditions, the performances under the other 4 conditions (left half figures in RHI and 3 kinds of figures in LHI), among which there were no significant differences, decreased significantly ($P < 0.01$ for each of the 8 comparisons).

When pointing to a target, Y.Y. moved his right hand slowly and stopped on figures one by one on a multiple-choice board. This tendency was conspicuous in performing left half figure trials in the RHI task and all trials in the LHI task.

Performance of the LHI task presumably reflected the degree of attention to the left halves of figures, since no differential information was placed in the right halves. Similarly, the performance in the RHI task reflected the degree of attention to the right halves of figures. The left hand scored well under any condition. As for responses with the right hand, the decrease in the scores in the LHI task suggested that Y.Y. oriented poorly to the left side. Of all the responses with the right hand in RHI, complete and chimeric figures had the highest averages of correct responses. These results suggest that he demonstrated good attention to the right side even with the right hand. In contrast, the significantly low score for left half figures with the right hand was considered to be attributable to imperfect visual perception, as suggested by the discussion of line bisection and confrontation naming during which he attended poorly to left half figures in the left hemispace.

Copying and reading aloud multiple digit numbers (August 1987)

The left hand revealed a behaviour that made us suspect mild neglect in right hemispace in copying multiple digit numbers.

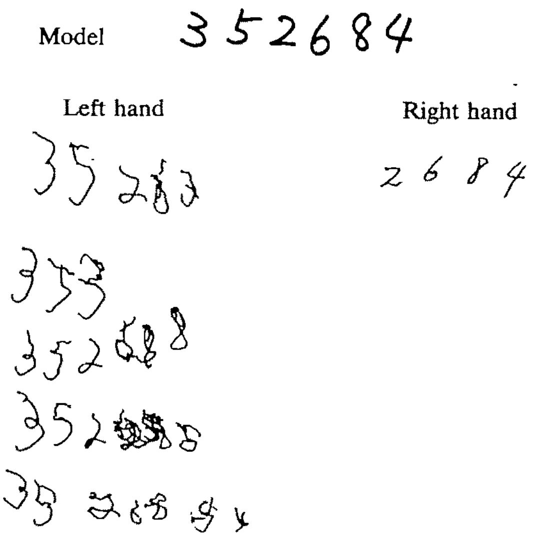


FIG. 8. Examples of responses in copying multiple digit numbers.

Methods

Y.Y. was asked to read aloud and copy numbers involving multiple digits, using a pencil held in either the left or the right hand. The numbers presented were written horizontally, 3 cm from the top, in the centre of a sheet of white paper (18 × 13 cm). Each digit was written by hand in black ink (2 mm thick), approximately 1.3 cm high and 1 cm wide including the space between digits. The stimulus numbers employed were from 1 to 6 digits. Three arbitrarily selected numbers were employed for every digit number. A total of 18 trials was performed. The order of the stimulus numbers and the hands used to execute the task was randomized. Copying accuracy was evaluated first.

Results and Discussion

Y.Y. copied the numbers from left to right with either hand. With 1 or 2 digit numbers, he revealed no abnormality with either hand. With more than 4 digits, his right hand neglected the leftmost 1 or 2 digits but copied the rest flawlessly in normal hand writing. In contrast, he successfully copied the leftmost 2–4 digits with his left hand. For the remainder, however, he repeatedly hesitated in his writing and/or wrote agraphically malformed digits which he strenuously tried to correct (fig. 8). In these circumstances, he was instructed to write again from the beginning or to write under the malformed digits. Sometimes anomalous stroke orders were observed that made us infer that he was copying digits as if he were drawing geometric or pictorial figures. The results of oral reading were almost the same as the ones with the right hand: he neglected the leftmost 1 or 2 digits of numbers with more than 4 digits, and read aloud the remainder without difficulty.

The poor replication of the leftmost digits in the multiple digit numbers, both in copying with the right hand and in reading aloud, can be considered in the same light as was observed in the above investigations. However, how can we interpret the poor replication of the rightmost digits while copying with the left hand? Right homonymous hemianopia can hardly explain this symptom because the right hand copied the rightmost digits flawlessly. Agraphia confined to the left hand cannot explain the fact that the same hand was able to copy some digits on the left side. We infer that the weakness in directional attention to the right side may be the cause of this right side symptom.

GENERAL DISCUSSION

Hemispatial neglect demonstrated by Y.Y. under nonlateralized testing conditions is summarized as follows. First, left hemispatial neglect was invariably shown not only in tasks performed with the right hand such as copying drawings, line bisection, matching identical figures, and copying multiple digit numbers, but also in tasks involving verbal responses such as confrontation naming and reading aloud multiple digit numbers. Secondly, equivocal right hemispatial neglect became apparent only when the left hand was mobilized for copying multiple digit numbers. Thus it is clear that conspicuous left hemispatial neglect occurred relative to the activities of the left hemisphere and little or no right hemispatial neglect occurred in relation to the activities of the right hemisphere. Since an apparent decrease in his responses to the left side was confirmed in the tasks where horizontal movement in visual searching and in pointing with the hands was minimized, such as in confrontation naming and matching identical figures, Y.Y.'s left-sided neglect was considered to be based on attentional deficits.

How can we interpret this symptom complex? Obviously, right homonymous hemianopia is not the explanation for the manifestation of severe neglect on the left side, because the hemispace in which salient neglect showed up was not on the right side. This suggests that neglect is not a mere sensory disturbance.

Secondly, it may be argued that the hemispatial neglect observed in Y.Y. was caused by unilateral intrahemispheric lesions. Certainly, there were low density spots which were considered to be lesions in the basal ganglia and thalamus of both hemispheres and the left medial frontal and temporo-occipital lobes. In the literature, left hemispatial neglect has been documented in association with damage in the region of the basal ganglia on the right (Damasio *et al.*, 1980), in the subcortical frontal lobe and basal ganglia on the right (Stein and Volpe, 1983), in the posterior limb of the right internal capsule (Ferro and Kertesz, 1984), and in the right thalamus (Watson and Heilman, 1979). Nevertheless, it seems difficult to ascribe left hemispatial neglect in our patient to the spots of low density in the right basal ganglia and thalamus. If these lesions are responsible for the development of left-sided neglect demonstrated conspicuously by left hemisphere activities, provided that the corpus callosum was intact then right hemisphere activities may be associated with left-sided neglect as well. In fact, the left hand did not show any left-sided neglect. Joanette *et al.* (1986) have observed that left-sided neglect was less severe with the left hand than with the right in right brain-damaged individuals with the least hemiparesis. The data for their 3 patients indicated that the left hand still showed prominent although less severe neglect. Weintraub and Mesulam (1987) also reported that manual exploration in patients with right hemisphere lesions, in whom the left hand was completely mobile, was less efficient within contralateral hemispace, regardless of the hand used. Furthermore, the cases of Sine *et al.* (1984) and Goldenberg (1986), who showed neglect signs confined to the right hand responses as well as varieties of callosal disconnection symptoms, had no lesion in the basal ganglia in either hemisphere. In light of these views, we surmise that Y.Y.'s left hemispatial neglect confined to left hemisphere activities is not attributable to the small hemisphere lesions.

Right hemispatial neglect, on the other hand, shown in left hand performance, if any, might be ascribed to the lesions in the parasagittal areas and/or the basal ganglia of the left hemisphere (Damasio *et al.*, 1980). If the right-sided neglect was a left hemisphere sign, there remains a question why left hemisphere activities did not demonstrate such right-sided neglect. This will be discussed later. In summary, marked dissociated manifestations of neglect between right and left hemisphere activities led us to infer that the neglect signs observed in Y.Y. could not be explained solely by his intrahemispheric lesions.

The remaining possibility is an interhemispheric disconnection. Note that he demonstrated various disconnection signs and had extensive lesions in the corpus callosum and the adjacent parasagittal hemisphere. Moreover, the dissociated manifestations of hemispatial neglect found between right and left hemisphere activities were observed. These findings strongly support an interhemispheric disconnection, which presupposes asymmetric cerebral representations of directed attention.

An adequate model of directed attention should be equipped with an explanation not only for the asymmetric manifestations of hemispatial neglect resulting from damage to the right or left hemispheres but also for such dissociated manifestations of neglect as observed in Y.Y. and the cases of Sine *et al.* (1984) and Goldenberg (1986). The asymmetrically directed attention model postulated by Heilman *et al.* (1980) and Mesulam (1981) explains the above two phenomena. This model may be compatible with the findings of Joanette *et al.* (1986) and Nishikawa *et al.* (1987) that the left hand tends to show milder left hemispatial neglect than the right hand in patients with right hemisphere damage. The contralaterally directed attention model with left hemisphere preponderance advocated by Kinsbourne (1977) fails to explain why, in our patient, right hemisphere activities were accompanied by little or no neglect in the right hemispace. The contralaterally directed symmetric attention model of Heilman *et al.* (1984) also fails to explain the same phenomenon. The bilaterally directed symmetric attention model of Plourde and Sperry (1984) also cannot explain the dissociated hemispatial neglect exhibited by Y.Y.

If such an asymmetry exists in the cerebral representation of directed attention, then it can be surmised that the brain is equipped with mechanisms for transmitting directed attention between the right and left hemispheres and also for modulating the whole. Suppose that the anatomical apparatus for the transmission is disturbed. The subject would have to depend predominantly on the left hemisphere when verbal or right manual performance was required. In this state, only the right-sided attention of the left hemisphere is activated while the bilateral attention of the right hemisphere is inhibited, thus resulting in the exclusion of left-sided attention. By the same logic, the subject has to depend on the right hemisphere when left manual performance is required. In this state, only the bilateral attention of the right hemisphere is activated while the right-sided attention of the left hemisphere is inhibited. As a result, the total amount of the right-sided attention may be decreased to some extent. Y.Y.'s symptomatology is consistent with these presuppositions and we may well interpret his neglect symptoms as a reflection of disturbances in the reciprocal transmission of attentional competence between the two hemispheres.

We should comment on the observation that the left hand showed mild right-sided neglect in copying multiple digit numbers. As discussed earlier, this may be ascribed to the lesions in the left medial frontal lobe. However, it is more likely that the right-sided neglect shown only by the left hand is also reflected by an interhemispheric disconnection. The capacity of the right hemisphere is preponderant in attending to the contralateral hemispace than to the ipsilateral hemispace where, as Mesulam (1981) anticipated, the left hemisphere is more preponderant. Thus we consider that the disconnection neglect syndrome, if any, has two types of neglect which are independently reflected by the shortage of the attentional capacities in each hemisphere. Further investigation is necessary to determine the capacity of the right hemisphere in ipsilateral hemispace.

How did the lesions in Y.Y. interfere with the transmission and modulation of directed attention? In light of the studies on commissurotomy patients, the lesions confined to the corpus callosum are unlikely to develop disconnection neglect. Y.Y., in common with the patients of Sine *et al.* (1984) and Goldenberg (1986), possessed lesions in the corpus callosum and medial frontal lobes. Y.Y. and the patient of Sine *et al.* (1984) had lesions in the medial part of the left frontal lobe, and the patient of Goldenberg (1986), bilaterally in the frontal lobes. It may be possible that intrahemispheric involvement, together with callosal involvement, is relevant to the occurrence of disconnection neglect. A similar view has been advanced with regard to disconnection apraxia. Yamadori (1985) pointed out that patients with spontaneous lesions in the corpus callosum, apparently accompanied by left hemisphere lesions, seem to develop far more severe apraxia than commissurotomized patients. The importance of medial frontal lobe damage for apraxia of the left limbs was also emphasized by Goldenberg *et al.* (1985).

Two reported cases with callosal lesions due to cerebrovascular disease have come to our attention. The patient of Heilman *et al.* (1984) showed the symptom designated as 'hemialexia' in reading compound words 3 days after the onset, which is presumably interpreted as a sign of left hemispatial neglect. Forty-four days after the ictus, these authors confirmed that the patient had no signs of hemispatial neglect. Meanwhile, improvement was also observed in language disturbance, palpatory naming difficulty with the left hand, difficultly in copying the alphabet with the left hand, and proximal leg weakness, which was presumed to have been caused by severe spasm of both anterior cerebral arteries. As the CT and MRI scans (Watson *et al.*, 1985) disclosed no evidence of cortical involvement, including the supplementary motor and cingulate cortices, the neuropsychological signs that subsided in the acute and subacute periods were attributed to transient dysfunction of the medial frontal lobes. Anatomical intactness of these regions might have contributed to her early improvement in 'hemialexia'. The patient of Nishikawa *et al.* (1988), diagnosed as cerebral infarction, did not show hemispatial neglect with either hand according to observations begun 5 wks postonset, although several disconnection signs were noted. The MRI studies disclosed lesions situated in the genu and trunk of the corpus callosum as well as minor lesions situated in the splenium and subcortically in front of the anterior horn of the left lateral ventricle. No major lesion was found in the medial cortices of either hemisphere. Our inferential argument is indirectly supported by these 2 cases.

The cerebral networks for attention may be represented widely from the brainstem to the forebrain cortex in the whole brain (*see* the network models of Heilman *et al.*, 1985) more widely than those for language. As a result, commissural fibres other than the forebrain commissure take part in the transmission of attentional information. Damasio *et al.* (1980) have suggested that the supplementary motor area and the anterior cingulate gyrus mediate information to and from the dorsolateral structures of the frontal lobe and subcortical components of the limbic system. Presumably, Y.Y.'s lesions in the left medial frontal lobe prevented transmission through the extracallosal commissures, which are spared in commissurotomy patients. It may be possible that lesions in the right medial frontal lobe play an identical role in producing disconnection neglect. Thus we propose that disconnection neglect would be attributable to a combination of lesions in the corpus callosum and in the medial frontal lobe.

On the basis of the discussion above, the following conclusions are derived. (1) The neglect symptoms observed in right manual and verbal performance provide evidence that the human capacity of directed attention is asymmetrically represented in the hemispheres. The right hemisphere is responsible for bilateral hemispaces although, possibly, less preponderant in the ipsilateral hemispace, while the left hemisphere only for the contralateral hemispace. (2) Hemispatial neglect may manifest as a disconnection sign in patients with callosal lesions resulting from cerebrovascular disease. It is suggested that a combination of lesions in the corpus callosum and in the medial frontal lobe is responsible for its manifestation, so that the capacities of directed attention represented in each hemisphere cannot be transmitted to the contralateral hemisphere.

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ADDENDUM

After this paper was accepted, we noticed further evidence for right hemispatial neglect in tasks of copying line-drawn cubes performed in October 1986 and May 1987 (fig. 9). A test sheet was presented only in central space and the rest of the procedures was the same as for testing the copying of line drawings (complete figures) as in the original report. Performances of the left hand were poor for the right side of the cubes. These observations are most likely based on the same mechanism as was inferred from the results in copying multiple digit numbers and thus further support our argument that the right hemisphere is less dominant in the ipsilateral hemispace.

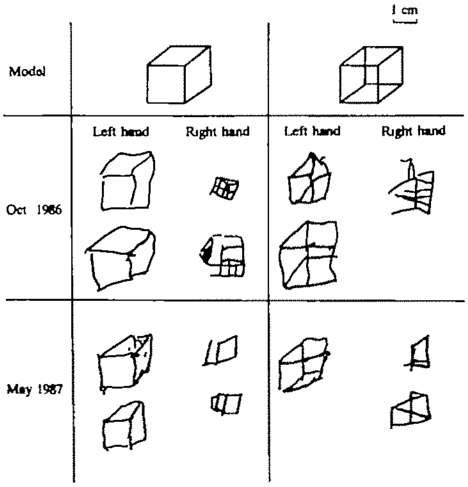

FIG. 9. YY's responses in copying line-drawn cubes, edited for demonstration.

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PERIPHERAL NEUROPATHY IN XERODERMA PIGMENTOSUM

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SUMMARY

The pathology of the peripheral nervous system (PNS) in 2 autopsied cases of group A xeroderma pigmentosum (De Sanctis Cacchione syndrome) are presented. Motor nerves including those of the oculomotor systems were severely affected, but involvement of the sensory system was even more marked. Minor hypertrophic changes were present in the distal portions of the peripheral nerve trunks, but there was no appreciable difference in the density of myelinated nerve fibres between proximal and distal levels. Morphometric data including teased fibre analyses and g ratio scattergrams suggest that the underlying pathogenetic mechanism is that of a neuronopathy. Unmyelinated axons were also severely depleted. Review of the previous literature revealed that the pathological changes of the PNS in group A xeroderma pigmentosum are thought to be slowly progressive, which is also suggested by the severe and widespread sclerotic changes of the CNS in the present 2 cases.

INTRODUCTION

Xeroderma pigmentosum (XP) is a group of autosomal recessive disorders related to a defect in the mechanism of DNA repair. It is characterized clinically by hypersensitivity to sunlight, which results in cutaneous pigmentary changes, including telangiectases, keratoses and eventually multiple cutaneous malignancies. There are nine complementation groups and a variant form within this disorder. Group A, the commonest in Japan, usually corresponds to the most severe clinical form of XP, and in most patients gives rise to involvement of the central and peripheral nervous systems in addition to cutaneous lesions, this combination comprising the De Sanctis Cacchione syndrome (De Sanctis and Cacchione, 1932). Some authors have pointed out that the involvement of the peripheral nervous system (PNS) in this syndrome is similar to that in Friedrich's ataxia (Yano, 1950) or neuropathy related to nutritional deficiency (Ogawa *et al.*, 1976); however, as there have been few autopsy reports, and as publications on the pathological changes in the PNS have usually been based only on biopsied material (Thrush *et al.*, 1974; Fukuhara *et al.*, 1982: Hakamada *et al.*, 1982; Origuchi *et al.*, 1987; Tachi *et al.*, 1988), the involvement of the PNS in this syndrome has not been completely clarified.

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Recently, we had the opportunity to investigate the pathological changes in the PNS in 2 autopsied cases of group A XP with neurological involvement. The aims of the present study were to examine the changes in the PNS, using morphometric methods, systematically from the spinal roots to the distal peripheral nerve trunks and to review the literature concerning the PNS pathology in this rare disorder.

CASE HISTORIES

Case 1

A.O., a male aged 19 yrs, was the product of a full term delivery with a birth weight of 2,915 g. There were no apparent abnormalities at birth. At the age of 1 month, prominent light sensitivity was noted and a diagnosis of XP was made when he was 5 months of age. He said a few single words at the age of 1 yr and attempted to walk at 18 months. When 10 yrs old, slurring of his speech developed and he showed a tendency to fall. These symptoms progressed slowly and he became bedridden when aged 15. He was admitted to the Tokyo Metropolitan Neurological Hospital for treatment of pneumonia at the age of 18 yrs.

Examination revealed microcephaly and prominent pigmentation of skin exposed to sunlight. Contractures of moderate degree had developed in the joints of all four limbs and he could only move his forearms slowly. There was severe muscle atrophy in all four limbs and fasciculation of the tongue was noted. All the tendon reflexes were absent and both plantar responses were extensor. Perception of visual, auditory and tactile stimuli persisted, but was gravely impaired. Motor nerve conduction velocity in the ulnar nerve was 40 $m \cdot s^{-1}$; sensory nerve action potentials were not obtainable.

He died at the age of 19 yrs because of intractable respiratory tract infection and acute renal failure. A postmortem examination was performed 2 h after death.

Case 2

S.H., a female aged 23 yrs, was the product of a full term delivery with a birth weight of 3,200 g. There were no apparent abnormalities at birth. At the age of 5 months, prominent light sensitivity was noted and a diagnosis of XP was made when she was 7 months of age. She said a few single words at the age of 1 yr. At the age of 7 yrs, mental retardation was noted (IQ = 64) and her hearing acuity was found to be slightly impaired. Dysarthria and gait disturbance developed by age 15, and the above symptoms had slowly increased. Her IQ was 30 at the age of 18 yrs and she became bedridden at age 22. She was admitted to the Tokyo Metropolitan Kita Medical and Rehabilitation Center for treatment of pyelonephritis and pneumonia.

Examination revealed short stature, microcephaly and hyperpigmentation of skin exposed to sunlight. She was alert but mentally retarded and could produce no intelligible words. Contractures of the joints of all four limbs had already developed. The upper limb tendon reflexes were diminished and those of the lower limbs were absent; both plantar responses were extensor. Her hearing was severely impaired, but the perception of somatic sensation was difficult to evaluate. Neither evoked muscle action potentials nor sensory action potentials were obtainable on stimulation of any peripheral nerve trunks. Brain CT revealed microcephaly with marked thickening of the skull.

At the age of 23 yrs, she suddenly died due to choking. A postmortem examination was performed 8 h after death.

In both cases, the diagnosis of group A XP was made during their lifetime on the basis of the results of cell complementation testing and studies on ultraviolet-induced unscheduled DNA synthesis in cultured skin fibroblasts.

MATERIAL AND METHODS

In addition to routine neuropathological examination on paraffin sections, morphometric and ultrastructural analyses were performed on the left C7 anterior and posterior roots, and the median, sural, sciatic and oculomotor nerves in both cases. The specimens were immediately fixed in phosphate-buffered 2.5% glutaraldehyde, postfixed in 1% osmium tetroxide and embedded in Epon.

Semithin transverse sections stained with toluidine blue were used for evaluation of the density and size distribution of myelinated nerve fibres. At least 3 fascicles at the same level were chosen randomly for photography in order to minimize sampling error. The total number of myelinated nerve fibres per nerve (or root) was determined for the oculomotor nerve, and the C7 anterior and posterior roots, and the density of myelinated fibres was for the median and sural nerves. Both the total number and the density of myelinated nerve fibres were evaluated in photomicrographs at ×500 magnification. The g ratios (ratio of axonal to total fibre diameter) were estimated in low power electron micrographs, which covered 0.10 mm^2 in XP cases and 0.03 mm^2 in controls, taken randomly, at a final magnification of ×2000.

Isolated single nerve fibres were prepared from specimens obtained from the L4 nerve roots and the sciatic and sural nerves. They were fixed in phosphate-buffered 2.5% glutaraldehyde and postfixed in 2% osmium tetroxide for 48 h, washed, and then immersed in graded (0–66%) concentrations of glycerin for 72 h. Except for the sural nerves of the XP cases, 100 fibres from each nerve were used for the grading of pathological changes according to the classification of Dyck *et al.* (1984).

Ultrathin sections were stained with uranyl acetate and lead citrate and observed under a JEOL 200CX electron microscope. The density and diameter of unmyelinated nerve fibres were determined from photographs which covered 0.02 mm^2 of the endoneurial area or more, taken randomly, at a final magnification of ×10 000. Unmyelinated axons were distinguished from Schwann cell profiles by their round or oval shape with mesaxon-like structures, according to the criteria of Ochoa and Mair (1969); any axon-like structures that did not fulfill these criteria were not counted.

Three patients (48 and 65-yr-old women, and a 56-yr-old man) who died following cerebrovascular lesions served as controls for the L4 nerve roots and the median, sciatic and sural nerves, and another 3 patients (56, 70 and 75-yr-old men) who died from cerebral infarction served as controls for the C7 nerve root and oculomotor nerve. Measurement of the myelinated and unmyelinated nerve fibre diameters, and statistical analysis were performed with a WT-4400 digitizer (Wacom KK) interfaced to a Nihon Denki PC9801VM personal computer.

RESULTS

Morphological abnormalities, including the results of quantitative analysis, were essentially similar in our 2 cases. The brains weighed 610 g (Case 1) and 580 g (Case 2). The pathological changes in the central nervous system (CNS), namely a widespread sclerotic cerebrocerebellar leucoencephalopathy (fig. 1) and moderate to severe neuronal loss in the cerebral cortex, thalamus, substantia nigra, pontine nuclei, inferior olivary nucleus and cerebellar cortex, was consistent with that described in previous articles (Yano, 1950; Reed *et al.*, 1977; Sasaki *et al.*, 1984; Röyttä and Anttinen, 1986). The dentatorubro-pallidoluysian system was relatively spared. The details of CNS pathology will be reported elsewhere.

Spinal cord

Changes in the spinal cord were only evaluated in paraffin sections. Anterior horn cells were severely decreased in number over the full length of the spinal cord (fig. 2).

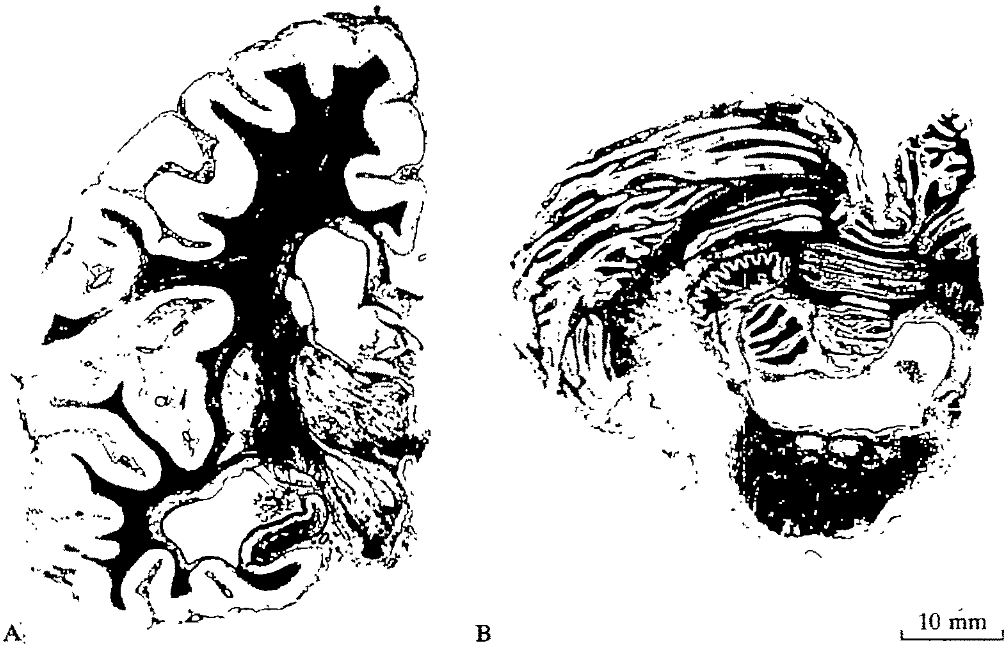

FIG. 1. *Case 2*. Widespread and severe fibrillary gliosis is present, especially in the cerebral white matter, thalamus (A), cerebellar white matter, dentate hilum and pons (B). Holzer stain.

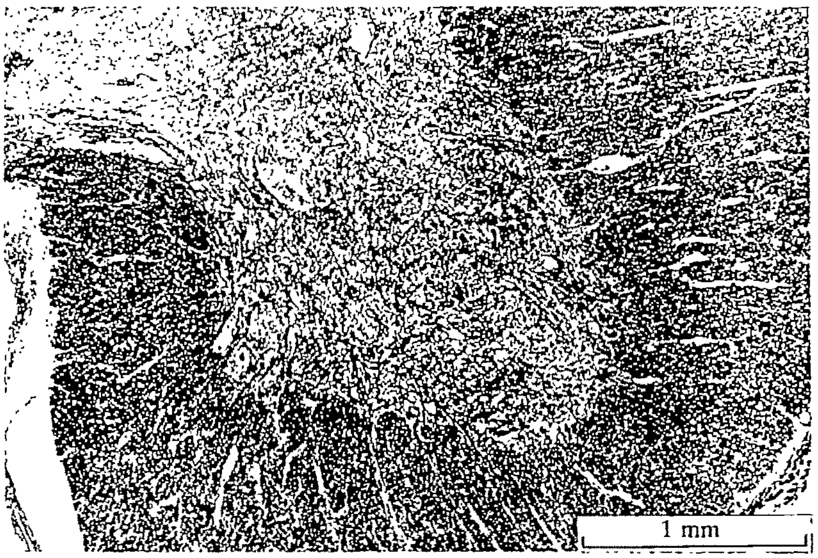

FIG. 2. *Case 2*. Severe depletion of anterior horn cells. L3 segment, spinal cord. Klüver-Barrera stain.

The number of neurons in Clarke's column was also decreased. Extremely severe loss of myelin and axons was noted in the posterior columns, and the anterior and posterior spinocerebellar tracts. In the posterior columns, there was no appreciable difference in the severity of involvement between the gracile and cuneate fasciculi, or between

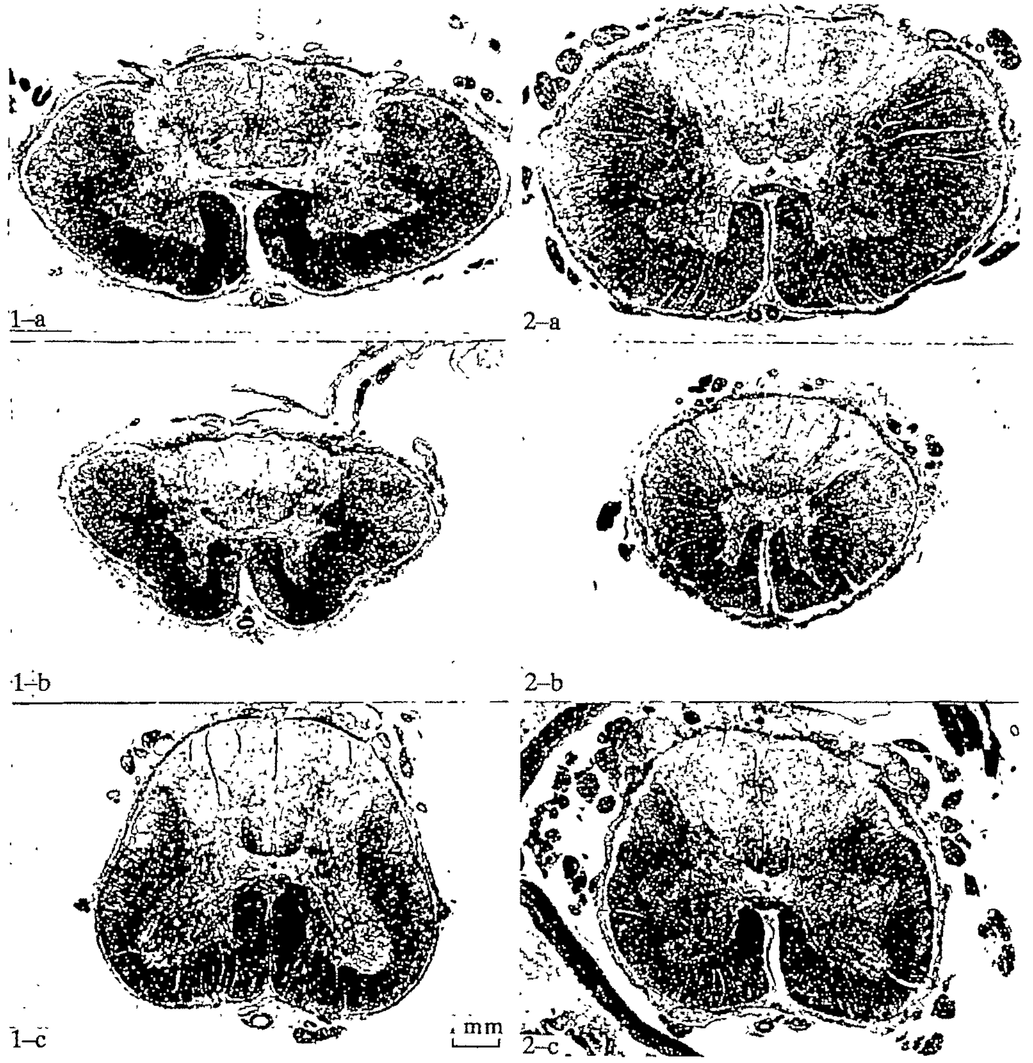

FIG. 3. Spinal cord. Prominent pallor can be seen in the posterior columns, and anterior and posterior spinocerebellar tracts. The severity of involvement of the posterior columns in the cervical cord (*upper*) is equal to that in the thoracic cord (*middle*) and that in the sacral cord (*lower*). 1-a, *Case 1*, C5 spinal cord. 1-b, *Case 1*, T3 spinal cord. 1-c, *Case 1*, S1 spinal cord. 2-a, *Case 2*, C5 spinal cord. 2-b, *Case 2*, T3 spinal cord. 2-c, *Case 2*, S1 spinal cord. Klüver-Barrera stain.

the cervical, thoracic and sacral regions (fig. 3). The lateral columns were also involved, although to a lesser degree. Dorsal root ganglion cells were severely depleted and numerous residual nodules were observed (fig. 4).

Peripheral nervous system

Light microscope observations. A prominent loss of myelinated nerve fibres was observed throughout the areas examined, but there was little evidence of active myelin breakdown, namely myelin ovoids, in the toluidine blue-stained semithin transverse sections. Myelinated nerve fibres loss was accompanied by marked endoneurial fibrosis in the peripheral trunks, whereas the total area of the nerve fascicles was considerably reduced in the spinal roots and cranial nerves; thus the density of myelinated nerve fibres in these areas was not as severely decreased.

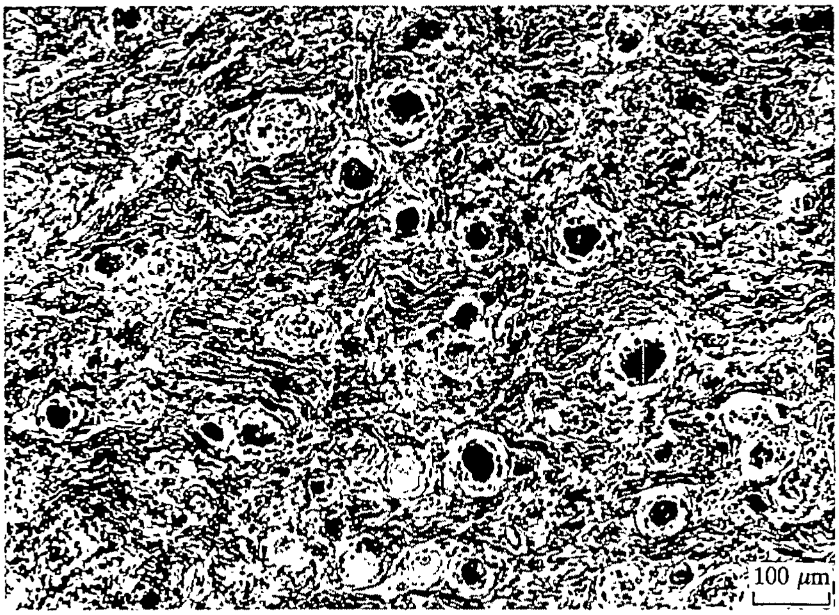

FIG. 4. *Case 2.* Severe involvement of posterior root ganglion cells. Residual nodules are abundant. Left C7 posterior root ganglion. Haematoxylin-eosin.

About 15–30% of the remaining myelinated fibres in the sural and distal median nerves showed a slight hypertrophic (onion-bulb) change (figs 5, 7B), although the proportion of fibres showing such change was under 10% in the proximal, median and sciatic nerves. In the spinal nerve roots, onion-bulb formations were observed only rarely. Many Renaut corpuscles were observed in the median nerve (wrist) of Case 2 (fig. 7B), a normal feature of the median nerve at this site.

Electron microscope observations. Collagen fibrils and denervated Schwann cell bands occupied the areas between the remaining myelinated fibres (fig. 5). Onion-bulb formations, which were most prominent in the sural nerves in both cases, were generally tiny and comprised only one or two whorls of concentrically arranged Schwann cell processes. Pi granules or 'zebra body'-like structures were occasionally seen in the cytoplasm of Schwann cells of the remaining myelinated fibres, but they had the same ultrastructure as those in normal nerves (Tomonaga and Sluga, 1970) and were not increased in number.

Unmyelinated axons were also decreased in number and denervated Schwann cell bands devoid of axons were abundant (fig. 6).

Morphometric analysis. As shown in Table 1 and fig. 7, the C7 posterior root was more prominently involved than the anterior root (88.6–90.7% vs 64.7–79.8% reduction). The reduction of small fibres was not as prominent in the anterior root because of a compensatory increase in small fibres present in regeneration clusters (fig. 7A, 2-b). In the posterior root, clusters of regenerating fibres were rarely observed and both small and large fibres were equally reduced in number. The oculomotor nerve also showed a severe depletion of both large and small myelinated nerve fibres.

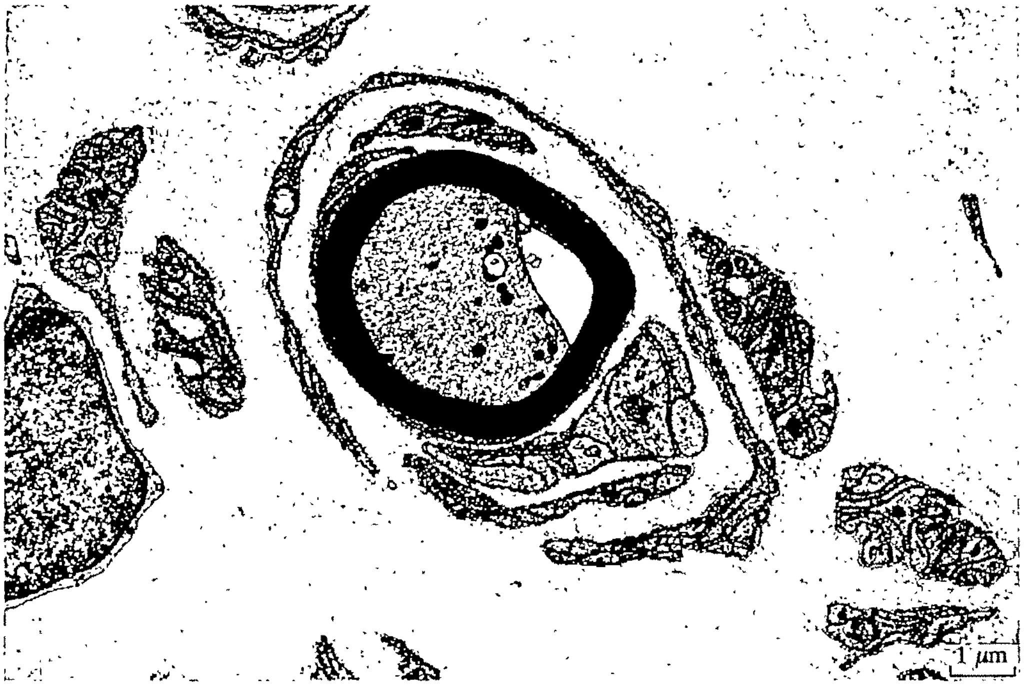

FIG. 5. *Case* 2. Some of the remaining myelinated nerve fibres show minor 'onion-bulb' changes, the Schwann cell processes surrounding the myelinated nerve fibres forming one or two concentric circles at most. Median nerve at wrist.

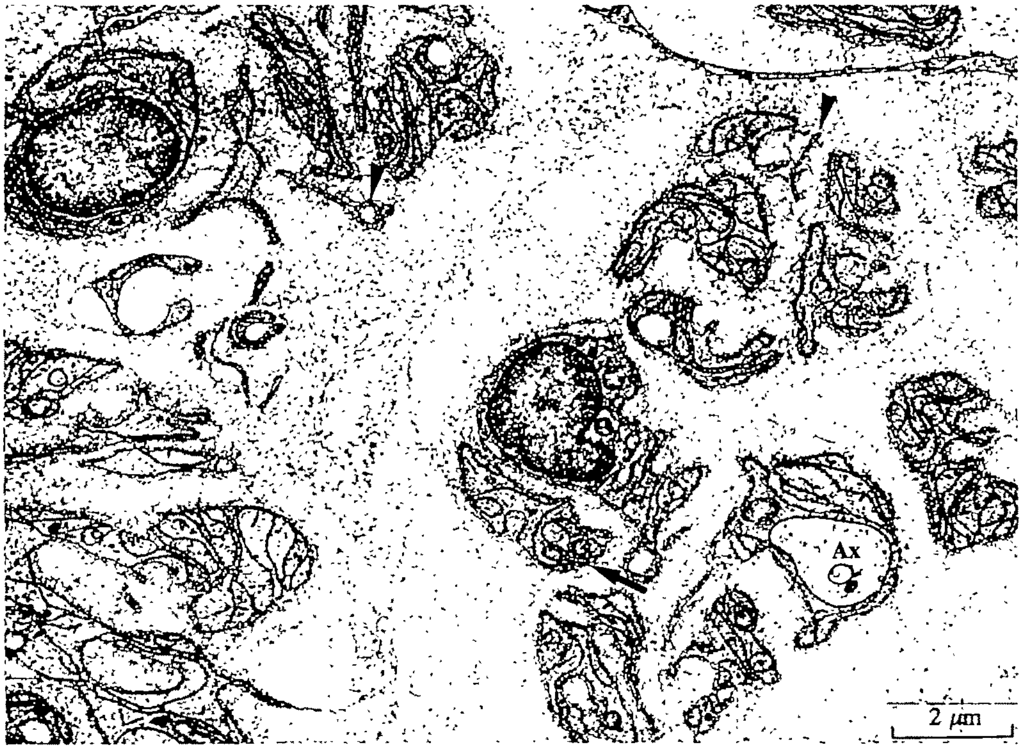

FIG. 6. *Case 2.* Schwann cell bands devoid of axons are abundant and there are few unmyelinated axons of normal appearance with mesaxon-like structures (arrow). The arrowhead indicates a residual basement membrane. Sural nerve.

TABLE 1. TOTAL NUMBERS OF MYELINATED NERVE FIBRES IN THE LEFT C7 ANTERIOR ROOT, C7 POSTERIOR ROOT AND OCULOMOTOR NERVE

	C7 anterior root			*C7 posterior root*			*Oculomotor nerve*		
	*Large**	*Small***	*Total*	*Large*	*Small*	*Total*	*Large*	*Small*	*Total*
Controls									
Mean	6,016	1,086	7,192	15,208	13,306	28,514	16,791	8,339	25,130
SEM	495	215	708	1,385	414	1,779	775	459	473
Case 1	923	528	1,451	943	1,718	2,661	1,317	794	2,111
Percentage loss	84.7	51.4	79.8	93.8	87.1	90.7	92.2	90.5	91.6
Case 2	1,492	1,045	2,537	1,306	1,953	3,259	4,281	1,261	5,542
Percentage loss	75.2	3.8	64.7	91.4	85.3	88.6	74.5	84.9	77.9

* Diameter $\geq$ 5.00 μm. ** Diameter $<$ 5.00 μm.

Table 2 shows the morphometric results for the main peripheral nerve trunks. The proximal and distal portions of the median nerve were equally involved. In the sural nerve (fig. 8), the density of myelinated nerve fibres was the lowest ever described for this disease (200 and 140/mm^2) and that of unmyelinated axons was also remarkably low (7100 and 4100/mm^2; fig. 9).

The scattergram of g ratios (axon diameter: total fibre diameter) for myelinated fibres in the sciatic, sural and median (proximal and distal portions) nerves are shown in fig. 10. Although the values in XP cases were reduced in number and were displaced to the area of small calibre, the variability of g ratios in XP cases was not increased as compared with that for the control case, either in the proximal or distal nerve trunks.

Teased fibre studies

Teased preparations of myelinated fibres demonstrated a few actively degenerating fibres with myelin ovoids (fig. 11) and also a few fibres showing segmental demyelination and remyelination. Compared with the controls, only the fibres showing the former change (axonal degeneration) were significantly increased in number (Table 3).

DISCUSSION

In addition to the CNS features, including microcephaly, progressive mental deterioration, deafness, ataxia and choreoathetosis, tendon areflexia and muscle wasting are the cardinal features of XP with neurological involvement. De Sanctis and Cacchione (1932) reported generalized areflexia in their patients in spite of extensor plantar responses; however, they ascribed them to involvement of the extrapyramidal system, and pathological or electrophysiological changes of the peripheral nervous system were not analysed until the 1970s. Festoff and Kraemer (1972) described for the first time delayed motor nerve conduction velocities and neuropathic EMG findings in this disorder, and Thrush *et al.* (1974) were the first to report a reduction in myelinated nerve fibre density in biopsied sural nerve. Subsequent studies confirmed their results electrophysiologically (Mimaki *et al.*, 1986) and morphologically (*see* Tables 4, 5); however, these results were insufficient for the elucidation of the pathological changes of the PNS as a whole, because the observations were limited to sensory (sural) nerves. Some of the previous authors briefly described the changes in the PNS in autopsied cases (*see* Table 4), but morphometric investigations were not performed in those studies; thus the changes of the PNS, over its whole length, remained unclear. The present work deserves to be reported because it provides basic quantitative data necessary for discussing the morphological background to the involvement of the PNS in this disorder.

With regard to the involvement of the spinal nerve roots, we found a greater decrease in myelinated nerve fibre numbers in the posterior than in the anterior root examined. Preferential involvement of the posterior roots, namely of the peripheral sensory system, had previously been reported by some authors in this disorder (Yano, 1950; Ogawa *et al.*, 1976; Sasaki *et al.*, 1984), and the results of our quantitative analyses confirmed this. A considerably milder reduction in the small fibres in the anterior root implies, probably, a relatively well-retained regenerative capacity of anterior horn cells in this disorder in contrast to that of posterior root ganglion cells.

The median nerve, sampled at the midhumeral portion and at the wrist, showed severe reductions in the myelinated nerve fibre density in both cases. On comparing the proximal and distal levels to determine whether there was a greater degeneration distally in the

PNS—which we had found in a case of type III Machado-Joseph disease, where there was a 89% loss of myelinated fibres at the wrist as compared with a loss of only 36% at midhumeral level (Kanda *et al.*, 1989)—we found no significant difference between the two levels. Ogawa *et al.* (1976) reported distal degeneration of the PNS in this disorder, but our results suggest that the pathological changes in the PNS in XP do not represent a distal axonopathy; possibly it is a secondary phenomenon following degeneration of primary sensory neurons and anterior horn cells, more especially of the former. The involvement of the posterior columns, equally severe over the whole length of the spinal cord and equally severe in the gracile and cuneate fasciculi, also supports this hypothesis. The rarity of the finding of active degeneration of myelinated fibres in the semithin transverse sections might be due to the chronicity of the pathological process.

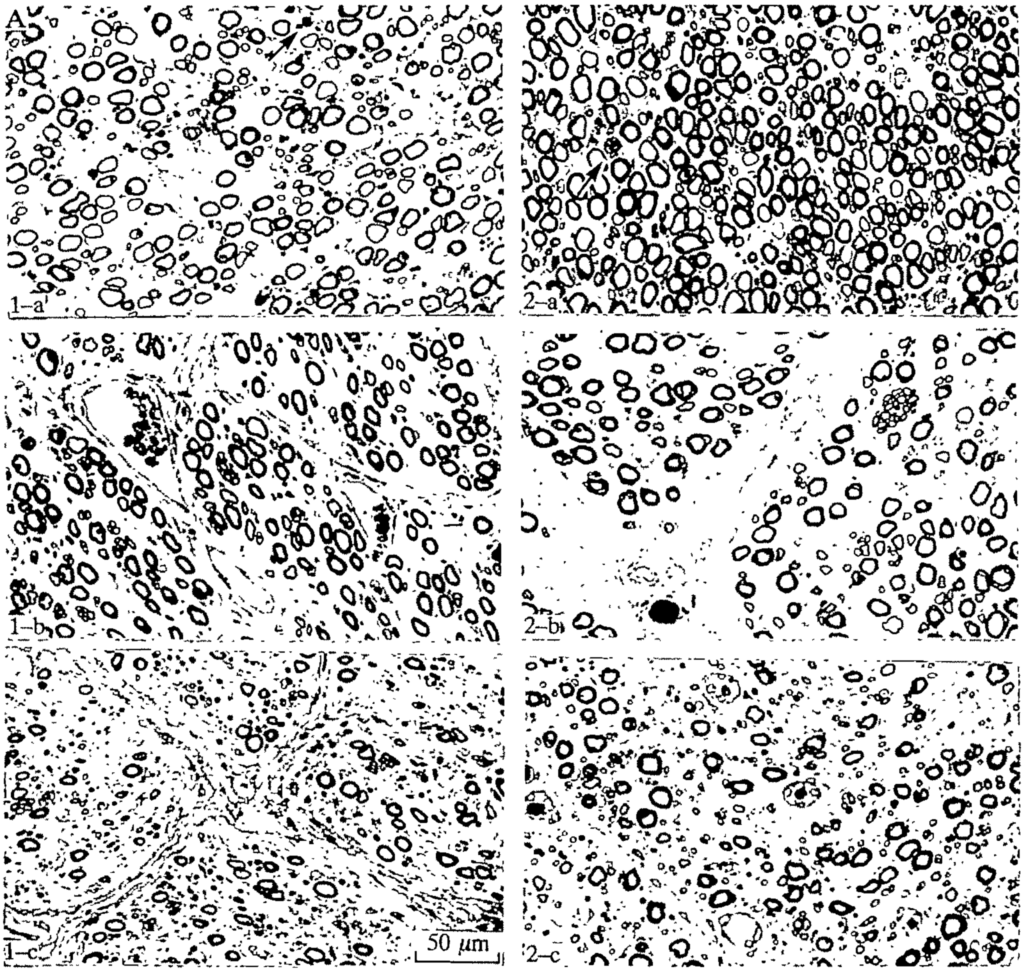

FIG. 7A.

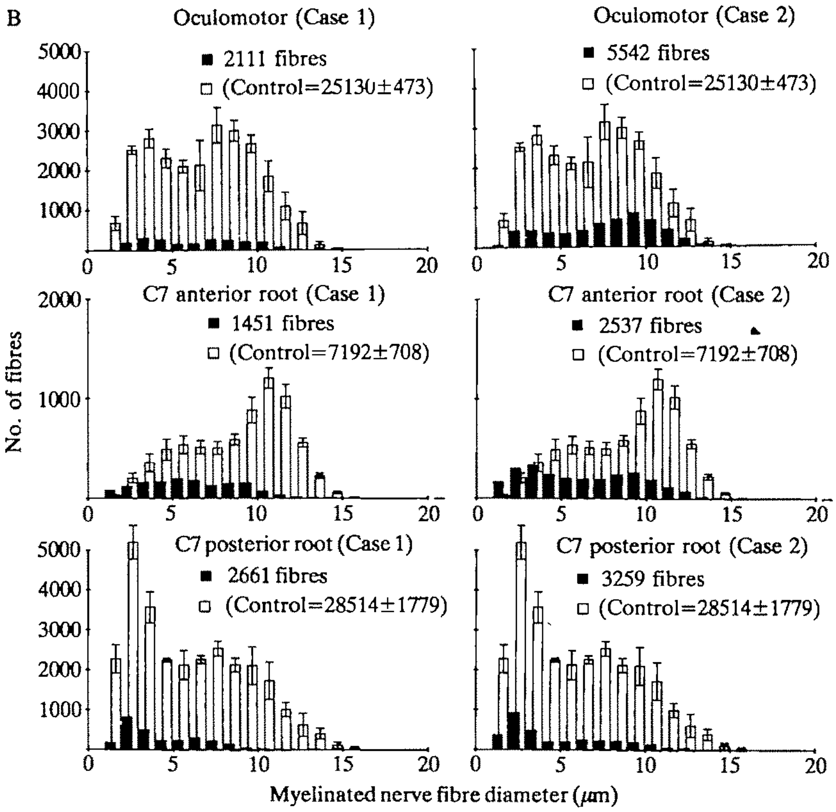

FIG. 7. A (opposite page), transverse semithin sections, toluidine blue stain, and B, corresponding histograms of the frequency distributions of myelinated nerve fibre diameters, for the oculomotor nerves (1-a, 2-a), C7 anterior roots (1-b, 2-b) and C7 posterior roots (1-c, 2-c) for *Cases 1 and 2* (black bars) and control cases (white bars). Error bars = SEM. *Case 1* shows more severe involvement. Myelinated fibre density in these sections does not appear to be greatly decreased, but the cranial nerves and spinal roots are exceedingly shrunken, and the total number of myelinated nerve fibres is severely decreased, especially in the posterior roots. A few myelin ovoids can be seen (arrows), but active axonal degeneration is rare, reflecting the chronicity of the disease process. Hypertrophic changes are not evident. *See* Table 1 and text for further explanation.

TABLE 2. DENSITIES OF MYELINATED NERVE FIBRES IN THE LEFT MEDIAN NERVE AND SURAL NERVE

	Median (midhumeral)			*Median (wrist)*			*Sural*		
	*Large**	*Small***	*Total*	*Large*	*Small*	*Total*	*Large*	*Small*	*Total*
Controls									
Mean	5,020	5,150	10,170	4,000	3,940	7,940	3,780	4,490	8,270
SEM	210	830	620	290	50	240	170	90	220
Case 1	362	523	885	329	442	771	35	165	200
Percentage loss	92.8	89.8	91.3	91.8	88.8	90.3	99.1	99.6	99.8
Case 2	625	1,449	2,074	562	896	1,458	28	112	140
Percentage loss	87.5	71.9	79.6	85.9	77.3	81.6	99.3	99.8	99.8

* Diameter ≥ 5.00 μm. ** Diameter < 5.00 μm.

A considerable amount of quantitative data concerning the sural nerve has accumulated for XP (Table 5). In the present 2 cases, myelinated nerve fibre density of the sural nerve was reduced to 140 and 200/mm^2, respectively; these are the lowest values reported for cases for which quantitative analysis has been performed. Scrutiny of the literature revealed that, in the Japanese cases, the density of myelinated nerve fibres decreased with the patient's age at the time of sural nerve biopsy (fig. 12A). Sasaki *et al.* (1984) reported a further reduction of myelinated nerve fibre density at autopsy, as compared with the biopsy data obtained 2 yrs before death. Mimaki *et al.* (1986) examined 32 patients with group A XP and reported that the knee jerk was normal in all 5 patients who were 2 yrs of age or under, whereas it was absent in 21 of 23 patients who were aged 7 yrs or older. This suggested that involvement of the PNS, including reduction in myelinated nerve fibre density in the sural nerve, is a slowly progressive

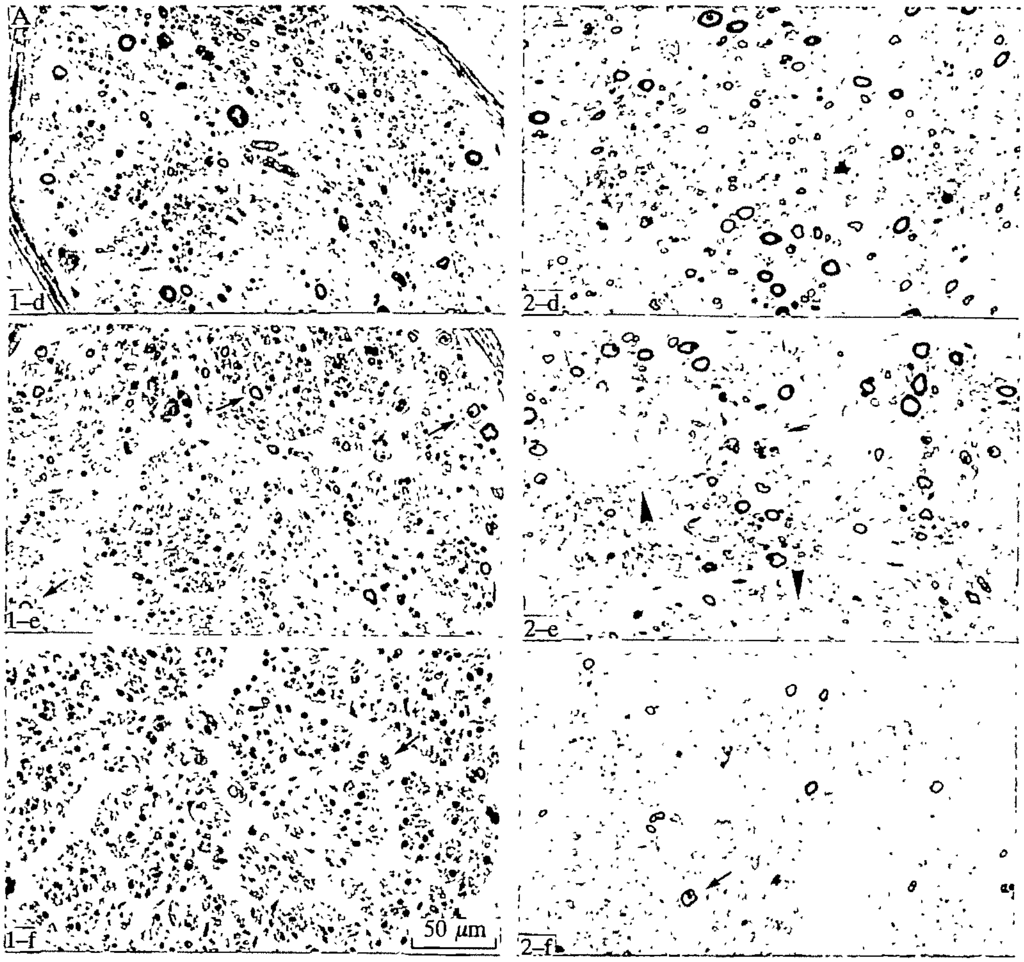

FIG. 8A.

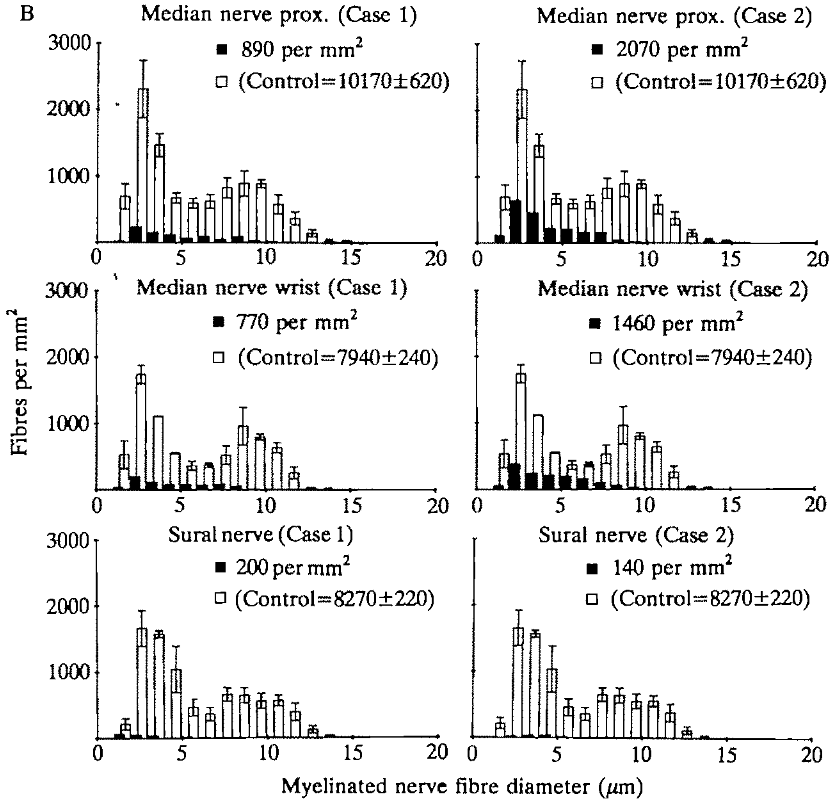

FIG. 8. A (opposite page), transverse semithin sections, toluidine blue stain, and B, corresponding histograms of the frequency distributions of myelinated nerve fibre diameters, for the proximal median nerves (1-d, 2-d), distal median nerves (1-e, 2-e) and sural nerves (1-f, 2-f) for *Cases 1 and 2* (black bars) and control cases (white bars). Error bars = SEM. Some of the remaining myelinated fibres show minor hypertrophic changes (arrows). The median nerve at the wrist in *Case 2* contains many Renaut corpuscles (arrowheads).

process; this may explain the severe reduction of the myelinated nerve fibre density in our cases, as they are the oldest among the Japanese cases for which quantitative data have been reported.

Fukuhara *et al.* (1982) commented on appearances in sural nerve biopsies which included separation of myelin lamellae and the presence of pi granules and dense bodies in the Schwann cell cytoplasm. Others have also commented on the presence of pi granules (Tachi *et al.*, 1988), but these structures are considered to be nonspecific and to have no special significance for pathogenesis. Hypertrophic changes have been noted in some patients (Fukuhara *et al.*, 1982; Origuchi *et al.*, 1987; Tachi *et al.*, 1988), as well as in the present cases. Their pathological significance in this disorder is difficult to determine just on the basis of sural nerve biopsies, because they are not only observed in primary demyelinating diseases such as chronic inflammatory demyelinating polyneuropathy (Dyck *et al.*, 1975), but also as the result of secondary demyelination due to axonal atrophy or following regeneration after axonal degeneration.

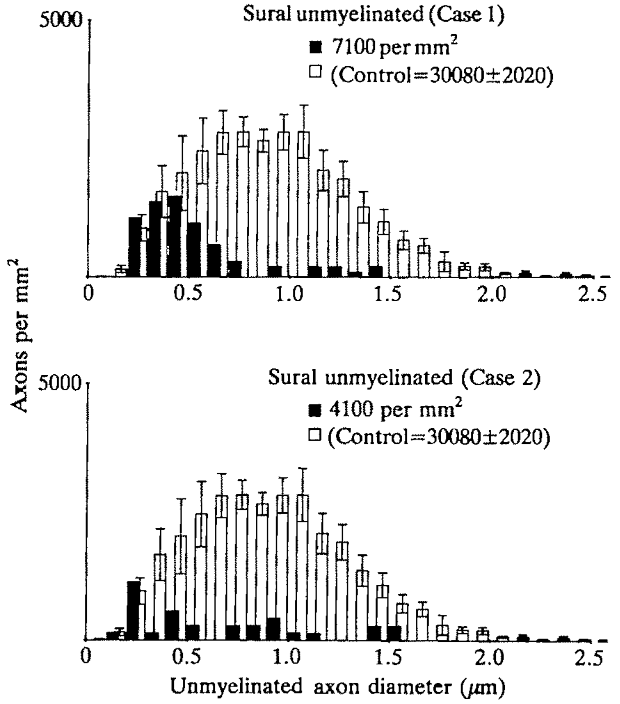

FIG. 9. Histograms of the frequency distribution for unmyelinated axon diameters in *Cases 1 and 2* (black bars) and control cases (white bars). Error bars = SEM. There is a severe depletion of unmyelinated axons.

In teased fibre preparations, we found a significantly increased number of fibres undergoing axonal degeneration in the lumbar nerve roots and sciatic nerve. Fibres which exhibited segmental demyelination and remyelination were also seen, but they were not increased as compared with the controls. We could not satisfactorily study the sural nerve, the most distal sensory nerve examined, because of the severe loss of myelinated fibres. However, comparing the teased fibre results for the lumbar roots with those for the sciatic nerve, we found no evidence for the presence of a distal axonopathy causing secondary demyelination with a peripheral accentuation. The variability in g ratios in the sciatic, sural, and proximal and distal median nerves was not increased. If secondary demyelination due to axonal atrophy had occurred, fibres with abnormally thick myelin sheaths and others with abnormally thin sheaths, indicating remyelination, would coexist, and increased variability in g ratios would be expected (Sobue *et al.*, 1989).

The morphometric results can be summarized as follows: (1) no significant difference between proximal and distal sites in the same nerve; (2) increased numbers of fibres undergoing axonal degeneration in teased fibre studies; and (3) no increase in variability of g ratios. In addition, the posterior columns were involved equally over the whole length of the spinal cord with no appreciable difference of involvement between the gracile and cuneate fasciculi. Considered as a whole, the principal disease process is

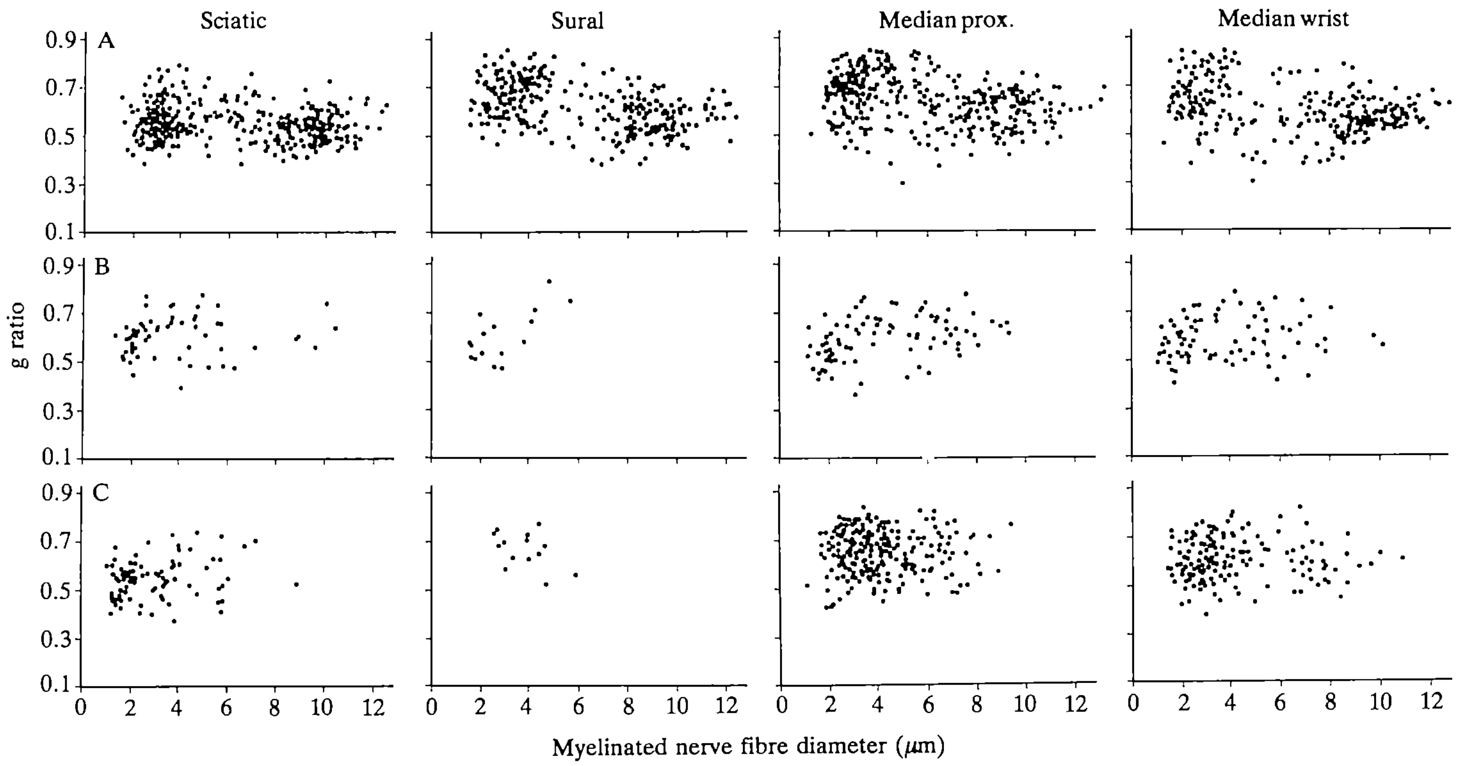

FIG. 10. Scattergram showing relationship of g ratio to fibre diameter for the sciatic, sural and median nerves (A, control; M, 56 yrs; B, *Case 1*; C, *Case 2*). The number of values in each scattergram corresponds to the number of myelinated fibres in 0.03 mm^2 in control and 0.1mm^2 in XP cases.

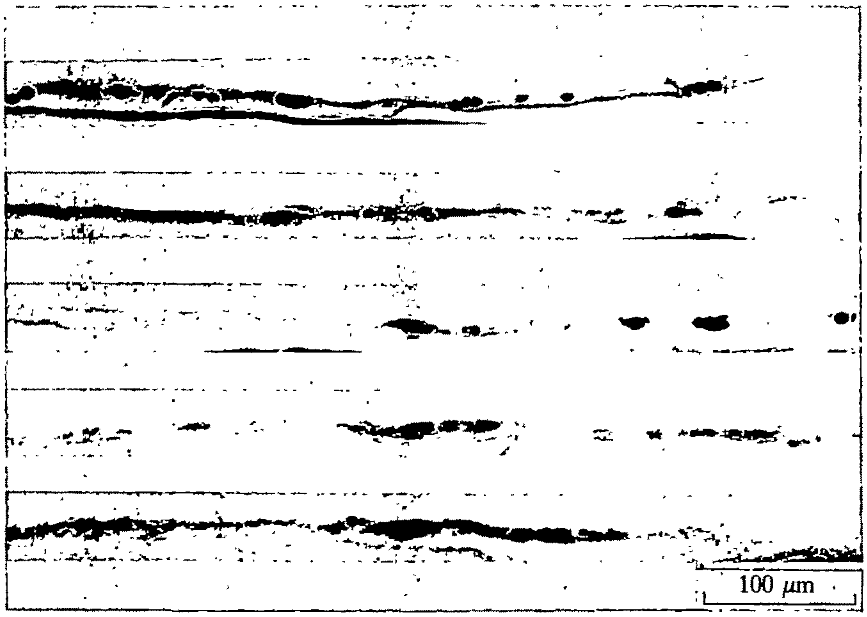

FIG. 11. Consecutive portions along the length of a single teased fibre from the sciatic nerve in *Case 1*. Myelin ovoids and balls of intermediate size are seen and each cluster is widely separated; this may contribute to the rarity of myelin ovoids in the transverse plane.

TABLE 3. TEASED FIBRE STUDIES

	Normal appearances or myelin irregularity (condition A and B)*	*Axonal degeneration and regeneration (E and H)*	*Segmental demyelination and remyelination (C, D, F and G)*
Sural nerves			
Case 1**	5 (100%)	0	0
Case 2**	6 (100%)	0	0
Controls	95.7±2.5 (93–98)	0.7±1.2 (0–2)	3.7±1.5 (2–5)
Sciatic nerves			
Case 1	92	6	2
Case 2	93	4	3
Controls	96.7±2.1 (95–99)	1.0±1.0 (0–2)	2.3±1.2 (1–3)
Fourth lumbar anterior roots			
Case 1	90	4	6
Case 2	92	3	5
Controls	95.3±1.2 (94–96)	0.3±0.6 (0–1)	4.3±1.5 (3–6)
Fourth lumbar posterior roots			
Case 1	90	4	6
Case 2	88	7	5
Controls	94.7±1.5 (93–96)	0	5.3±1.5 (4–7)

* Classification of Dyck *et al.* (1984). ** Sural nerve specimen contained very few myelinated nerve fibres and only 5 (Case 1) and 6 (Case 2) could be teased. Control values are expressed as mean ± SD with range in brackets.

that of a neuronopathy, with no morphological evidence of a primary Schwann cell derangement or secondary demyelination due to axonal atrophy. Thus the minor 'onion-bulb' changes are thought to be formed as the result of regeneration after axonal

TABLE 4. PATHOLOGICAL CHANGES OF THE PERIPHERAL NERVOUS SYSTEM IN DE SANCTIS CACCHIONE SYNDROME

	Yano (1950)			*Reed et al.*	*Ogawa et al.*	*Lewis et al.*	*Sasaki et al.*	*Röytta et al.*	*Present cases*	
	Case 1		*Case 2*	*(1969)*	*(1976)*	*(1978)*	*(1984)*	*(1986)*	*Case 1*	*Case 2*
Age, sex	*15, M*		*22, F*	*14, F*	*19, M*	*41, F*	*17, M*	*32, F*	*19, M*	*23, F*
Anterior horn cells	ND		ND	−	+	ND	+	+	++	++
Posterior root ganglia	++	<	++	ND	++	++	+	ND	++	++
Anterior root	−		−	ND	+	ND	+	ND	++	++
Posterior root	++	<	++	ND	++*	ND	+*	ND	++*	++*
Peripheral nervous system	ND		ND	ND	++**	ND	++	++	++	++

* The posterior root was more severely involved than the anterior root. ** Distally dominant degeneration of the peripheral nervous system. − = not involved; + = mildly or moderately involved; ++ = severely involved; ND = not described.

TABLE 5. MORPHOMETRIC DATA ON SURAL NERVES IN DE SANCTIS CACCHIONE SYNDROME

		Biopsy (b) or autopsy (a)	*Age, sex*	*Myelinated nerve fibre density (per mm^2)*	*Unmyelinated axon density (per mm^2)*
Thrush *et al.* (1974)		b	27M	2,220	ND
Muramoto *et al.* (1981)		b	18M	975	48,200
Fukuhara *et al.* (1982)	1	b	11F	3,324	83,643
	2	b	12F	1,276	38,559
	3	b	15M	772	16,940
Hakamada *et al.* (1982)		b	16M	742	ND
Sasaki *et al.* (1984)	1	b	15M	1,042	57,130
	*1	a	17M	556	ND
Nakamura *et al.* (1987)		b	11F	1,100	5,450
Origuchi *et al.* (1987)	1	b	6M	5,163	46,234
	2	b	7F	5,808	55,612
Tachi *et al.* (1988)	1	b	11M	9,620	65,306
	2	b	12F	2,300	35,918
	3	b	15F	2,900	37,224
	4	b	17M	1,042	21,250
Present cases	1	a	19M	200	4,100
	2	a	23F	140	7,100

* Both a biopsy (2 yrs before death) and a postmortem examination were performed on this patient.

degeneration. The small numbers of concentric circles of Schwann cell bands surrounding the myelinated nerve fibres would also favour this conclusion.

Quantitative analysis of a sural nerve biopsy in a non-Japanese case has only been performed by Thrush *et al.* (1974). Although the genetic form in their case was not reported, his neurological deficits as well as the decrease in myelinated nerve fibre density (fig. 12A) were slight for his age, and it is suggested that he belonged to a complementation group other than A, probably group D, another common subgroup in Europe (Kraemer *et al.*, 1987).

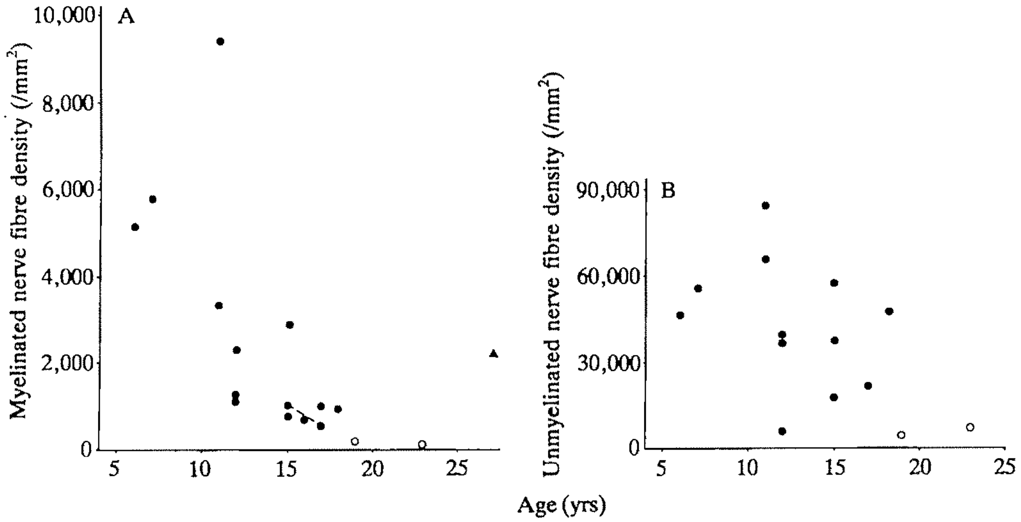

FIG. 12. The relationship between the myelinated fibre (A) and unmyelinated axon (B) densities and age in XP. Solid circles indicate Japanese cases described by previous authors and open circles the present 2 cases. The solid triangle indicates the European case reported by Thrush *et al.* (1974). The 2 solid circles linked by the interrupted line represent the case described by Sasaki *et al.* (1984), in which autopsy material was also obtained 2 yrs after the biopsy, when a further decrease in the myelinated nerve fibre density was evident.

Some previous authors have reported a decrease in the density of unmyelinated axons as compared with age-matched controls, especially in older patients (Fukuhara *et al.*, 1982; Tachi *et al.*, 1988), and pointed out a tendency for diminution in axon diameter (Muramoto *et al.*, 1981). Considered as a whole, however, no significant correlation between unmyelinated nerve fibre density and the patient's age is evident (fig. 12B), in contrast to the age-dependent diminution apparent for myelinated fibres. However, when comparing the density values for unmyelinated axons given in the literature, attention should be paid to the variability in the criteria used for the detection of unmyelinated axons by the authors; tiny Schwann cell processes without mesaxon-like structures might have been counted as unmyelinated axons in some previous studies.

In the present 2 cases, unmyelinated axons were recognized according to the above-mentioned criteria (Ochoa and Mair, 1969) and normal appearing unmyelinated axons were very few in number, in contrast to the abundance of flattened denervated Schwann cell processes. Involvement of unmyelinated axons in hereditary neuropathies with a diminution of their number has been reported in only a limited number of disorders including the Riley-Day syndrome (Aguayo *et al.*, 1971), Fabry's disease (Ohnishi and Dyck, 1974) and familial amyloid polyneuropathy (Thomas and King, 1974). In contrast to these disorders, impairment of the sensory modalities associated with unmyelinated axons in the De Sanctis Cacchione syndrome was difficult to assess because of the severe dementia and hearing loss. Although evidence of an age-dependent diminution in density was not obtained, involvement of unmyelinated nerve fibres in the De Sanctis Cacchione syndrome is definite, especially in older patients such as the present 2 cases.

The cause of the involvement of the PNS as well as the CNS in this disorder cannot as yet be adequately explained. Although the PNS is considered not to be directly reached by ultraviolet light and careful avoidance of direct sunlight does not prevent the development of nerve damage, a disturbance in the process of DNA repair is believed to be implicated in the pathogenetics of the neural lesions, because neurons that have been damaged for any physiological or biochemical reason may lose the capacity to synthesize critical enzymes or other proteins necessary for their function or survival, as suggested by Robbins *et al.* (1974).

Ataxia telangiectasia is another disorder which shows defective DNA repair. Although no systematic and extensive study on the pathology of peripheral nervous system, as performed in the present study on XP, has yet been performed in this disorder, it has been reported that biopsied sural nerve shows a decrease in myelinated nerve fibre density (Schoonderwaldt *et al.*, 1973; Okamoto *et al.*, 1981) and that the electrophysiological findings also suggest a primary axonal rather than a demyelinating process. The similarity of the pathological picture in the PNS between XP and ataxia telangiectasia may favour the conclusion that a common pathogenetic mechanism, probably neuronal cell death due to defective DNA repair, exists in both. The investigation of this possibility must be the subject of future research, and extensive analyses of the pathology of the PNS, including morphometry, should be accumulated in these two disorders.

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PRESERVED RECALL VERSUS IMPAIRED RECOGNITION

A CASE STUDY

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SUMMARY

A very pure and most unusual case of memory impairment is reported in a patient operated on for an aneurysm of the anterior communicating artery. Neuropsychological investigation performed about 8 yrs after the operation revealed a dissociation between very poor performance on recognition tests (on which the patient's performance was as poor as that in classical amnesic patients) and normal performance (estimated by the number of correct responses) in recall. This pattern has not previously been reported and is the reverse of that observed both in normal subjects and in amnesic patients. In addition, the patient was able to achieve a number of difficult learning tasks, at times normally; the relearning of one of these tasks after a delay of 1 h was perfectly normal. The recognition failure is interpreted in terms of the suggestion that memory performance results from an interaction between knowledge and subjective experience of remembering.

INTRODUCTION

In the course of the past 10 yrs, a large proportion of studies in cognitive neuropsychology has been based on the principle of modularity. This principle (as described by Marr, 1976) postulates the functional independence of modules, namely hypothetical subsystems brought into play in certain types of task. This principle makes it possible to imagine that a cerebral lesion can destroy or disorganize an isolated cognitive subsystem without necessarily disturbing the functioning of the other subsystems involved in the same task. In principle, therefore, we can try to identify the hypothetical components that are disturbed and those which remain potentially functional in a given patient. This approach has been used in a large number of studies in the field of reading, writing and speech disorders and has been carried out with some success. There have, however, been few applications in research on amnesia, perhaps owing to the multiplicity of the models proposed, which are not all based on the principle of modularity, and which are sometimes difficult to compare at the experimental level. Although research has increasingly emphasized the multiplicity of clinical forms of amnesia, in particular those linked to aetiology or to the location of the lesion, few studies have as yet described the cognitive syndromes which might make it possible to establish the functional independence of a

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given subsystem involved in the memorization and retrieval of information. There are strong arguments in favour of a dissociation between long-term and short-term memory (for a review, *see,* e.g., Shallice, 1979, 1988), between verbal and nonverbal representations (*see* Paivio, 1986), and between different nonverbal modality-specific forms of representation (e.g., Beauvois, 1982). There are also arguments in favour of Tulving's (1972) distinction between episodic and semantic memory (Lhermitte and Signoret, 1972; Warrington, 1975; Tulving, 1983*a*). On the other hand there are, to our knowledge, no neuropsychological arguments in favour of a dissociation between two processes of retrieval, one involved in recall, the other in recognition. Indeed, in amnesia, it is often claimed that, if anything, recognition is superior to recall (Hirst *et al.*, 1986), which would appear to indicate that both tasks involve the same processes, but that recognition is simply easier to perform than recall. If, however, the two tasks involve distinct processes, it should be possible to find a converse dissociation. It is the second of these two points that interests us here.

This paper describes the study of a patient who, following an operation for anterior communicating artery aneurysm, produced a normal number of correct responses in tasks of recall, whereas his performance was comparable to that of amnesics in recognition tasks; this constitutes a dissociation that has not hitherto been observed. Whether this argues in favour of two distinct retrieval processes will be discussed.

Previous studies have also focused on the memory of patients suffering from an aneurysm of the anterior communicating artery. The performance of these patients is nonhomogeneous, since it is sometimes normal or almost normal on certain tests (Kapur and Coughlan, 1980; Vilkki, 1985; Parkin *et al.*, 1988; Janowsky *et al.*, 1989) or, on the other hand, highly disturbed (Stuss *et al.*, 1978; Damasio *et al.*, 1985); moreover certain patients produce numerous confabulations (Talland *et al.*, 1967; Luria, 1976; Stuss *et al.*, 1978; Kapur and Coughlan, 1980; Damasio *et al.*, 1985; Vilkki, 1985; DeLuca and Cicerone, 1989; Youngjohn *et al.*, 1989), whereas others do not appear to do so (Luria, 1976; Volpe and Hirst, 1983; Parkin *et al.*, 1988). This heterogeneity is, a priori, hardly surprising. First, it is known that closely comparable lesions may affect different physiological systems. Secondly, the assumption of modularity, and the complexity of the processes involved in memory performance, lead us to expect extremely varied disturbances of processing, which ought to take on distinct clinical forms—which emphasizes the importance of case studies.

CASE REPORT

History

R.W., a right-handed man, was born in 1927. He was raised as bilingual in French and English. He obtained the baccalaureat, although his education suffered several interruptions because of the war. Then he entered a new merchant banking group and because of his initiative and drive, rapidly became one of the managing directors. He was actively involved in sports.

On February 26, 1973 (at the age of 46 yrs) he was admitted to the Hôpital La Pitié-Salpêtrière in a stage 3 coma. An acute hydrocephalus was drained by canulation of the right lateral ventricle. His level of consciousness gradually and progressively improved until he regained full consciousness 20 days after the onset. At this time he was able to smile but had a left hemiplegia with a right frontal abnormality on EEG. He was operated on (by Professor Pertuiset) on March 26. The operation was carried out using a right frontotemporal approach. An aneurysm of the anterior communicating artery was clipped. The site was moderately unusual in that it arose from the junction of the pericallosal part of the right anterior cerebral artery and the anterior communicating artery. The aneurysm extended laterally to the left and lay posterior to the pericallosal portion of the left anterior cerebral artery. The surgical approach to the aneurysm was by way of the frontal poles both of which appeared to be infarcted. The infarct on the right was more extensive and extended into the inferior surface of the lobe.

The patient was examined at La Salpêtrière in January, 1974. At that time neurological examination was entirely normal. However, he showed intellectual impairment (Progressive Matrices below the 25th centile; Performance IQ on the WAIS 75) and from a severe memory impairment (MQ 86 on the Wechsler Memory Scale). There was no evidence of aphasia, apraxia or agnosia. Using a method described by Derouesné *et al.* (1975) an attempt was made to rehabilitate certain cognitive functions, working mainly with the Progressive Matrices and the Block Design subtest of the WAIS. However, no attempt was made to rehabilitate the patient's memory disturbances. He left Paris in 1975 and tried to take up his former work but was totally unable to do so. He therefore remained at home. In other respects his everyday life was in general normal, going out with friends and to the cinema, reading, watching TV, writing the story of his life as a novel, and making a collection of French jokes.

In 1981 the authors contacted him and it was decided to visit him at home, as he lives far from Paris. R.W. underwent a further complete neuropsychological examination together with a detailed investigation of his memory impairment during 1981 and 1984, that is, more than 8 yrs after his operation.

A CT scan was performed in November 1980, that is, more than 7 yrs after the operation. It was analysed by Dr A. Musolino, according to a previously described method (Musolino *et al.*, 1987). An area of hypodensity (*see* fig. 1) was seen on cuts 1–7 (i.e., 6–57 mm). On the two lower cuts (6 and 11 mm) the hypodensity affected the right temporal pole (i.e., the anterosuperior part of the temporal gyrus and the anterior part of the fusiform gyrus). On cut 3 (20 mm) there was bilateral involvement, more extensive in the right hemisphere, of the rectus gyri, together with hypodensity of the orbital parts of the second and third frontal gyri and of the frontal operculum on the right. On cut 4 (25 mm) the hypodensity involved the subcallosal and anterior parts of the cingulate gyri and the anterior and medial parts of the superior frontal gyri bilaterally (but more in the right hemisphere); it also affected the right frontal operculum. On cut 5 (34 mm) the hypodensity affected the anterior and medial parts of the superior frontal gyri bilaterally, together with the anterior and precallosal parts of the cingulate gyri; it also involved the right frontal operculum. On cut 6 (47 mm) the hypodensity affected the anterior parts of the superior frontal gyri and the superior and anterior parts of the cingulate gyri bilaterally. On cut 7 (55 mm) it involved the medial parts of the superior frontal gyri and the anterior parts of the cingulate gyri bilaterally. In summary, there was a large area of hypodensity affecting (1) the medial parts of both frontal lobes (rectus gyrus, the anterior and subcallosal part of the cingulate gyrus, and the medial and anterior part of the superior frontal gyrus), the hypodensity being more extensive in the right hemisphere where there was involvement of the frontal operculum and of the medial part of F2 and F3; (2) in the right hemisphere, both the temporal pole and the internal part of the fusiform and parahippocampal gyri.

Neuropsychological examination

Intellectual efficiency

R.W. performed very well on certain tasks which are in general considered to be sensitive to intellectual deterioration such as the Progressive Matrices (above 90th centile) for which he had received rehabilitation in 1974, and D 48 (Pichot, 1961) (IQ 118) on which no rehabilitation has been carried out. However, as far as his WAIS performance was concerned, there was a minor abnormality since he obtained a Verbal IQ of only 102 and a Performance IQ of 87 (*see* Table 1).

Language

Oral expression. Speech appeared to be normal; articulation, intonation and fluency were correct and sentences were properly constructed. There was no paraphasia. R.W. repeated all the syllables, words and sentences of the Examen de l'Aphasie (Ducarne de Ribaucourt, 1976) entirely correctly and also the sentences of the Terman Merrill Intelligence Scale at the highest level. Retrieval of words was easy and accurate: he was able to name 47/50 pictures of objects and 19/20 sounds of objects; he was also able to produce the opposite of a given word quickly (50/50 correct) and in the Vocabulary subtest of the WAIS word definitions were in the normal range (*see* Table 1). He was able to construct 6/7 sentences from 2 given words. Five min passages of speech on topics such as his job and his family were recorded and

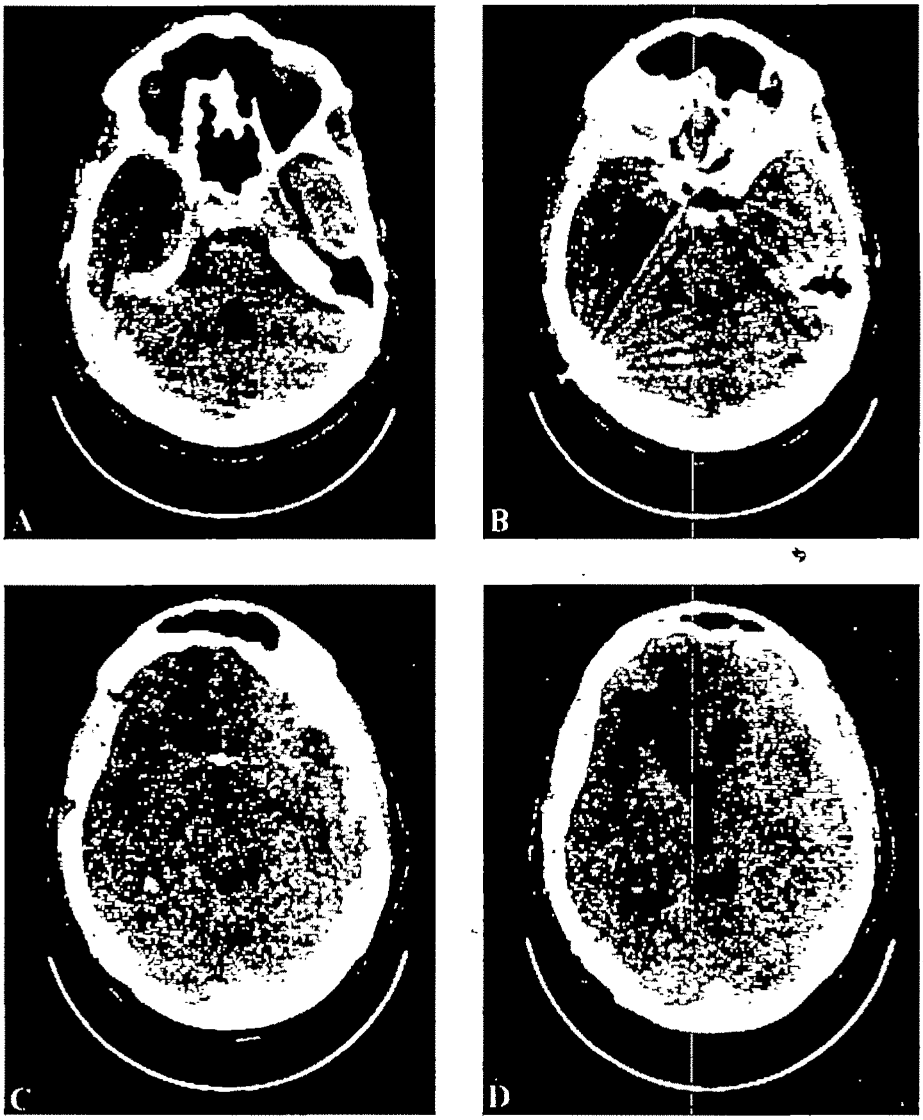

FIG. 1. A–D.

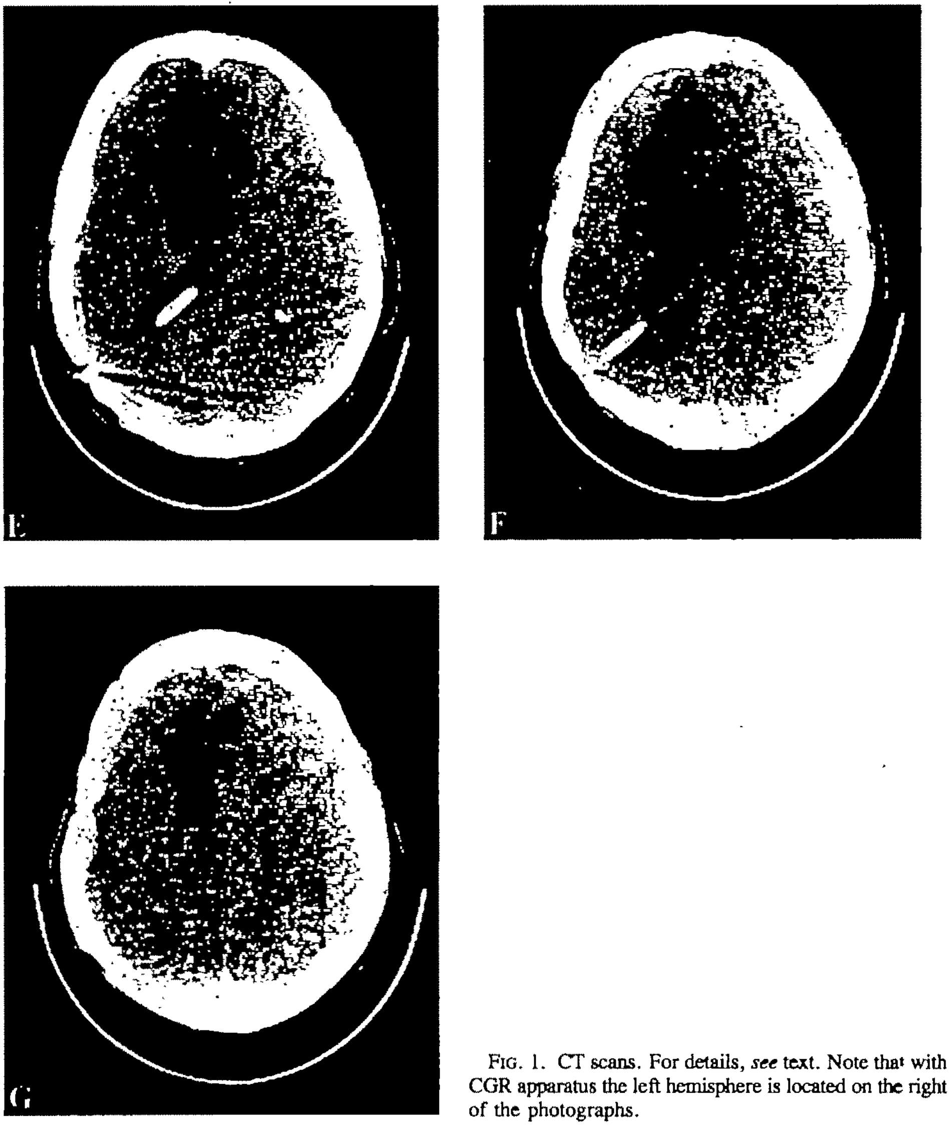

FIG. 1. CT scans. For details, *see* text. Note that with CGR apparatus the left hemisphere is located on the right of the photographs.

analysed: he produced 614 words concerning his work, a similar amount to that obtained by Shallice and Butterworth (1977) for normal subjects. His verbal expression can therefore be considered normal.

Understanding of oral language. This was also very good. He obtained a maximum score on all the tests of oral understanding of the Examen de l'Aphasie, on the French version of the Picture Vocabulary Test (Légé and Dague, 1976), on a test of comprehension of verb-inflexions (60/60), on the critique of irrational stories of the Terman Merill Intelligence Scale and on the most difficult part of the Token Test (De Renzi and Vignolo, 1962).

Reading. Reading aloud was very good as shown by his performance on a variety of tests involving irregular words (71/72), nonwords (20/20), and a text specially designed to detect minimal reading difficulties

TABLE 1. STANDARD SCORES ON WAIS SUBTESTS

Information	11
Comprehension	10
Arithmetic	10
Digit span	11
Vocabulary	11
Digit symbol	7
Picture completion	10
Block design	7
Picture arrangement	10
Object assembly	4

in French (Alouette Reading Test; Lefavrais, 1967) on which he achieved the highest level, since he read the 265 words of the text in 2 min 20 s with only 2 errors. Comprehension of written material was also good. This was shown for content words (by his IQ of 117 on the Synonym Test (Binois and Pichot, 1958), for verb inflexions (60/60), for syntactic elements of sentences including function words and word order (20/20) and for difficult sentences in general (22/22 on the most difficult part of the written form of the Token Test).

Writing. On the whole the patient's writing abilities were good. One of his favourite activities was to write drafts of books. His writing to dictation was fairly good both for irregular words (47/50) and for long and difficult nonwords (19/20) such as 'Biroufrignou'.

Visual processes

A number of tests were administered to R.W. in order to assess his ability to process visual material. First there was no sign of visual neglect: he performed perfectly and quickly on tests of marking all the examples of a particular stimulus on a page (22/22 for letter A in 35 s, 20/20 circles in 55 s), on a test of bisection of lines (11/11) and showed no lateral bias on a test based on the Visual Searching Test of De Renzi *et al.* (1970). On Thurstone's (1963) Test of Identical Forms, a speed test based on the principle of a shape being matched with 1 of 5 visually similar shapes, he obtained a score of 19 which is near the mean for people younger in age (40–49 yrs). Object recognition appeared to be intact: he named 45/50 perceptually difficult pictures of objects correctly, which is a satisfactory level of performance. On the test developed by Pillon and Lhermitte (1978), where the subject has to recognize an object from a figure in which the amount of information is progressively increased, his score was 109; this was in the mean range of the control subjects without brain lesions.

His ability to process colours and coloured stimuli was investigated. He had normal results on the Ishihara pseudoisochromatic plates (38/38), on the Farnsworth-Munsell 100 Hue Test, and on a test of colour naming (19/20).

He could recognize only 15/20 famous faces; this was clearly abnormal.

Visuospatial and constructional abilities

The patient was able to copy adequately a house, the drawings of a Bender Gestalt Test and the Rey Figure (type 1, above 90th centile). However, his attempt to copy a cube was poor and his scores on the Block Design and on the Assembly subtests of the WAIS were only in the dull normal range (*see* Table 1). His score on a test which involved spatial analysis but not reproduction was normal: he scored 14/16 on the Block Counting (or Cube Analysis) Test (Terman and Merill, 1960). R.W. therefore probably suffered from a minor impairment of constructional abilities, which might account for his rather low Performance IQ on the WAIS.

Motor behaviour and praxis

No grasping reflex, utilization behaviour (Lhermitte, 1983) or motor neglect was present. There was no sign of apraxia: handling of objects on spoken request (20/20) and miming the use of objects on spoken request (20/20) were carried out correctly. Imitation of single meaningless gestures was also carried out correctly with the right hand (13/13), the left hand (13/13) and both hands (15/15). However, in performing symbolic gestures on spoken request the patient had minor difficulties, obtaining only 13/15 with the right hand and 11/15 with the left. In everyday life his motor activity appeared on the whole to be normal: there were no signs of apathy, and he used to take long walks to go to the cinema or to visit friends. The only apparent change in his motor activity was that he had given up skiing and playing tennis since his stroke.

Body image

R.W. showed no evidence of asomatognosia. In particular, he could point out 20/20 parts of his own body on spoken request.

Calculation

The patient knew the multiplication tables fairly well and was able to perform mathematical calculations mentally. He produced the solutions to verbally proposed problems in a normal fashion (*see* Table 1).

Tests considered sensitive to frontal lesions

As R.W. had a lesion involving frontal lobe structures, his performance was assessed on tasks involving functional systems thought to be sensitive to frontal lobe lesions.

Sequencing tests (Luria, 1966). Three of these tasks were administered to R.W. In the first two, he was asked to learn (1) four sequences of figures of length 2, 3 and 4 (e.g., triangle, diamond, circle, square); (2) two sequences of gestures, one of length 2 and the other of length 3. After learning he was asked to repeat each sequence a specific number of times, first in the order of presentation and then in the reverse order. In the third task, R.W. was asked to repeat 5 series of 3 and 4 syllables, first in the order of presentation and then in reverse order. In the three tasks all sequences were completely correctly reproduced in the original order. On the reversed condition he made errors on 4/11 sequences (2 with figures and 2 with syllables). All were minor except for 3 perseverations in one sequence. Considering his performance as a whole, R.W.'s deficit on these tests was minor.

Other tests. Ten other tests considered to be sensitive to frontal lobe dysfunctions were performed with R.W. On six of them his performance was strictly normal. Indeed, five of them—Weigl's Sorting Test; Wisconsin Card Sorting Test, using Nelson's (1976) version; Luria's (1966) Drawing-to-a-Rule Test, Tapping Rhythms Test and 'Alternation Test'—were carried out without a single error and R.W.'s score on the sixth (Tower of London Test; Shallice, 1982) was within the normal range.

On two tests his performance was only a little slower than that of control subjects: on Armitage's Trail Making Test (1946), as used by E. K. Warrington, T. Shallice and F. L. Watson (personal communication); on Luria's (1966) Bilateral Hand Movements Test, as used by Warrington, Shallice and T. R. Oldfield (personal communication). On another, Luria's Verbal Control of Tapping (1966), R.W. made one error only. It was only on the task of Word Fluency, using the version of Ramier and Hécaen (1970), that R.W.'s performance was clearly abnormal. The test involves generating as many words as possible in 1 min, starting with the letters F, P and L. His performance—an average of 9.7 words generated—was roughly half that achieved by brain damaged controls (right hemisphere nonfrontal lesions) in Ramier and Hécaen's study and similar to that obtained by their left frontal nonaphasic group.

To summarize, R.W. showed little evidence of cognitive impairment associated with frontal lobe lesions since, out of 13 tests known to be sensitive to such lesions, only 1 was clearly impaired.

Tests of attention

Tests of attention also might reveal impairment following a lesion of the frontal lobes. Two were given to R.W. as a disturbance of attention might have an effect on his performance on memory tests. The first (Tests des Deux Barrages; Zazzo, 1979) is a test of concentration and attention. The subject has to cross out as quickly as possible every example of one sign (first condition) or of either of two signs (second condition) on a page of similar signs. In the first condition R.W. was able to monitor 1000 signs in 9 min, making only 6 omissions and no errors. In the second he monitored 450 signs in 10 min, making only 10 omissions and no errors. No norms are available for subjects of his age. However, by comparison with a group of normal subjects aged 20 yrs, he did not make significantly more errors. On the second test, R.W. was asked to keep in mind 6 digits for 1 min with no distraction. He performed correctly on 8 occasions out of 10, which can be considered normal.

Clinical test of memory

On the Wechsler Memory Scale (*see* Table 2), R.W.'s MQ was 94, which is in the dull normal range and not significantly different from his IQ on the WAIS. On Logical Memory, confabulations occurred, for example, 'a daily help' was changed into 'a Spanish daily help', 'Place de la République' into 'gare de Lyon', 'the officers made a purse for her' into 'very likely she was put in prison', '18 women' into 'women and children' and 'blinding snowstorm' into 'fog'.

Semantic memory

For most of the tests involving semantic memory, R.W.'s level of performance was completely normal. These tests involve various kinds of semantic knowledge: linguistic, visual, arithmetic, historical and geographical. However, in the second group of tests, smaller in number than the first, his performance was marred by surprisingly gross errors. These tests were the following: naming of famous faces, pointing out the correctly coloured object, performing symbolic gestures on spoken request, the WAIS Information subtest, drawing of the map of France, giving dates or producing chronological ordering both of historical facts and of the calendar. One illustrative example of the kind of confabulations produced by R.W. in his retrieval of semantic-memory information can be found in the way he told the story of Little Red Riding Hood (*see* Appendix 1) (e.g., 'a grand-mother who was called LRRH'). For a particular piece of information, R.W. often gave several responses, being sometimes correct and sometimes wrong.

Autobiographical memory

Autobiographical memory was investigated clinically by recording about 4 h of questions and conversations with the patient. As far as possible, every point of information given by the patient was checked with his wife. R.W. suffered from retrograde amnesia, the duration of which was roughly estimated at several months. It was more clearly perceptible in recall (in which he remembered nothing) than in recognition. For remote memory, R.W. was able to produce a detailed account of his childhood and adolescence. His wife judged that all the important events of his life had been correctly described, with one exception: R.W.'s reports concerning dates, durations and chronology which varied from one evocation to the other, were sometimes correct and sometimes incorrect.

Recall of recent events, either social or personal, was most often correct. However, a number of confabulations were recorded in his recall of both personal and social events (*see* Appendix 2).

TABLE 2. R.W.'s SCORES ON THE SUBTESTS OF THE WECHSLER MEMORY SCALE

	R.W.'s raw scores	*Mean for his age*	*SD*
Personal and Current Information	6	5.9	0.61
Orientation	5	4.95	0.27
Mental Control	6	6.44	2.47
Logical Memory	5.5	9.81	4.39
Digit Span	11	10.12	2.32
Visual Reproduction	5	9.38	3.73
Paired Associate Learning	18	15.61	4.23

Awareness of the disturbance

One of the characteristic features of R.W. concerns the nature of his awareness of his memory difficulties (*see* Appendix 3). He explicitly and constantly admitted to having suffered from retrograde amnesia of several months. In contrast, he never explicitly admitted to having any ongoing difficulties with memory as a consequence of his operation.

Summary

Aged 46 yrs, R.W., the managing director of a bank, was operated on for an aneurysm of the anterior communicating artery, which was clipped. Eight years later, the lesion on the CT scans appeared to involve the medial part of the frontal lobes. Neurological examination was normal. Neuropsychological examination revealed certain mild difficulties (in constructional abilities, performance of symbolic gestures on spoken request, recognition of famous faces and certain tests sensitive to frontal lesions) together with memory impairment. Clinically, the impairment took the form of a disturbance of remembering, mainly characterized by confabulations, of which he seemed to be unaware. However, R.W.'s MQ on the Wechsler Memory Scale remained in the dull normal range.

Investigation of R.W.'s memory

Tasks of short-term memory

R.W. obtained normal results on various short-term memory tests: different kinds of span, two forms of missing scan tasks and two tests of retention during short intervals using the Brown-Perterson procedure (see Baddeley and Warrington, 1970).

His span for different types of material was within 1 SD of the normal mean: 7 with digits, 6 with letters, 5 with syllables, 4 with two-syllable words (Beauvois and Lhermitte, 1975), 4.1 with Corsi Blocks (De Renzi *et al.*, 1977).

Two different kinds of missing scan task were used in order to test his ability to concentrate throughout a working memory task. In each case 10 trials were given for each span length (range 3 to 8). In the first form (Buschke's standard form, 1963), the experimenter gave all but one of the first x digits (e.g., for a span of 4 if the experimenter said 2.4.1., the subject must say 3). The second form was similar to normal span except that at the time of retrieval the experimenter said the digits again, omitting the one that the subject had to retrieve (e.g., if the series was 7.9.4.1 the examiner said 7 . . . 4.1., and the subject must say 9). On the first form, R.W.'s performance was above the mean of 4 control subjects of the same age, for all string lengths (the overall mean was 93% for R.W. and 80% for control subjects). On the second form his performance was again better than the mean of the 4 control subjects, for all except one of the string-lengths (6) (the overall mean was 92% for R.W. and 86% for control subjects).

Short-term retention over short intervals involving a filler task was tested with the Brown-Perterson procedure, using two forms, one involving words, the other involving letters. We used the same method as that adopted by Baddeley and Warrington (1970) in their study on amnesic patients, except that the filler task was more demanding: the subject was presented with cards on which two-digit numbers were printed and had to add one to each number as quickly as possible (on average one number every 1.9 s). With words R.W. performed much better on this task than the means of both the amnesic patients and the control subjects of Baddeley and Warrington's study. With letters he again performed much better than Warrington's (1982) controls.

Control groups for the following memory test

For many of the tests which follow it is possible to compare R.W.'s performance with that of 75 subjects (divided into 5 age ranges and 3 cultural levels). These tests were specially designed for the study of R.W.'s memory impairment. Indeed, at the time, there were virtually no experimental tests of memory available in French with a sufficient number of control subjects. However, the number and type of control subjects is crucial in the use of memory tests, since the dispersion for this kind of test is quite often very large. The use of a control group of 75 subjects allows more robust comparisons than those obtained with the procedure typically used in individual case studies (i.e., a small control group); in particular it allows the use of the percentile principle which is not dependent upon assumptions of underlying normality in the distribution of test scores. Results on the 75 control subjects, together with the way they are affected by age and cultural level are reported in Delbecq-Derouesné and Beauvois (1989). The control group consisted of cells of 5 subjects in each of the 5 age ranges and each of the 3 cultural levels. R.W. lay in the middle range as regards cultural level but in the fourth of the 5 age ranges. If, therefore, there was an effect of age on the results of the battery, his performance was compared with that of two populations: the group of 75 and also the group of 15 of equivalent age. R.W.'s performance was considered abnormal when his score was equal to, or worse than, the one obtained by less than 6% of the control subjects (3 out of 75 and 0 out of 15). It was considered to be at the limit of (i.e., just within) the normal range when his score was equal to, or worse than, the one obtained by less than 12% of the control subjects (8 out of 75 and 1 out of 15). Where results of the test battery are not available, the more usual procedure of comparing the patient's performance with that of a small group of matched controls is used.

Tasks of recognition

Eight tasks of recognition after a single presentation were carried out. Since R.W. had a frontal lobe lesion, a potential impairment on recognition tests might have resulted from a failure of attention or motivation (even though this is not obvious on other tasks) rather than from a true memory failure. In order to compensate for such possible impairments of attention or motivation, the recognition tests used had the two following characteristics: (1) an orienting task was used; (2) all but one of the tasks were tests of incidental memory.

Forced-choice recognition tests. On these tests, 50 items were presented one after the other for 3 s each, together with the orienting task used by Warrington (1984) (the patient had to say whether he found the item pleasant or unpleasant). He was not told that his memory of the items would be tested. Following the presentation of the 50 items, memory of the items was tested using a two-alternative forced-choice recognition procedure. Four different forms were used: in one the stimuli were words; in two they were faces of the sets used by Warrington (1984, and personal communication); in the fourth they were abstract paintings. The faces tests were carried out using four different procedures with two sets of photographs (*see* Table 3). The first was the procedure described by Warrington (1984). The aim of the second was to check whether a possible deficit on recognition tests might be due to a failure to follow instructions or to distractibility (the patient might have responded not to the face he remembered, but to the one he thought the more pleasant); at the time of retrieval, therefore, the retrieval instructions were repeated when each test pair was presented. In the third procedure the patient had to make a confidence judgement ('I'm

TABLE 3. FORCED CHOICE RECOGNITION TEST[1]

	Faces						
	Set 1			*Set 2*		*Paintings*	*Words*
Conditions	1	2	2	3	4		
Dates	November 81	December 81	December 84	July 84	December 84	December 84	November 81
R.W.	32	34	34	30	34	38	34
75 control subjects	1-0-74*	2-1-72*	2-1-72*	1-0-74*	2-1-72*	0-0-75**	
15 control subjects	0-0-15*	0-0-15*	0-0-15*	0-0-15*	0-0-15*	0-0-15*	0-0-15*

[1] The table gives first, the condition which was used for the recognition of faces (1 = standard condition used by Warrington; 2 = repetition of the instructions at the time of recognition; 3 = recognition associated with a confidence judgement; 4 = explicit instructions of memorization); secondly, the date when the test was carried out; and thirdly, R.W.'s scores; then, the number of control subjects out of the 75 who had a score less than, equal to and greater than R.W.'s and the probability of being incorrect in assuming that R.W.'s score is abnormal (*$P < 0.06$; **$P < 0.01$); the last line is equivalent to the previous one, with the exception that R.W.'s scores are compared with those of the 15 control subjects of the same age.

TABLE 4. R.W.'s CONFIDENCE JUDGEMENT FOR CORRECT AND INCORRECT RESPONSES ON THE FORCED-CHOICE RECOGNITION TEST FOR FACES

	Certain	*Maybe*	*Guessing*
Correct responses (30)	19	6	5
Incorrect responses (20)	15	5	0

sure', 'maybe', 'I don't know') after each trial. In the fourth, he was given an explicit instruction to memorize before the beginning of the test.

On all these recognition tests R.W. performed just above chance or within the chance range. He performed significantly below the normal range, both by comparison with our control groups and by comparison with those of Warrington (1984). On the test where comparable versions were used (namely, words and faces) he performed within the range reported by Warrington and Weiskrantz (1978) for amnesic subjects. None of the experimental manipulations altered R.W.'s pattern of results. This means that his very abnormal results on recognition tests were not due to problems of attention or motivation, or to forgetting what he had to do at the time of retrieval, or to the use of incidental memory.

A very interesting pattern of results emerged when confidence ratings were used (*see* Table 4). R.W. gave the response 'I'm sure' quite frequently. He was at least as certain that he was correct when in fact he had chosen the wrong item (he said he was sure for 75% of these items) as when he had given the correct response (he said he was sure for 67% of these). Whereas he admitted he had guessed 5 correct responses, he did not admit to having guessed a single incorrect response. R.W. therefore showed pathological confidence in his incorrect responses. This was confirmed when the tapes of the forced-choice recognition tests were analysed: R.W. had made rapid choices, and almost always responded without hesitation. He had shown no signs of uncertainty and had never attempted to correct his response once he had given it.

Three additional analyses were performed. In the first, it was shown that the patient's pattern of performance did not vary between the first part of the retrieval period and the final part. Therefore, there did not appear to be any fatigue factor relevant to his recognition deficit. Secondly, R.W.'s pattern of responses, like that of control subjects, was not affected by whether the items were rated pleasant or unpleasant. Finally, it was wondered whether the patient's answers at the recognition stage might be due to the fact that he found one of the two pictures presented more pleasant than the other. In other words, instead of responding to the picture, might he have responded to the one that he found the more attractive. To check this, on one occasion after the recognition test, R.W. was asked to point to the face he found the more attractive: he pointed to the one he had recognized on only 28 trials (not different from chance).

Two years later a control experiment was carried out with the test involving abstract paintings. The series of 50 items was administered three times consecutively. R.W.'s score (41) was not significantly higher than with only one presentation (38). However, a very interesting result occurred: R.W.'s rating (pleasant or unpleasant) was consistent over the three presentations for 39/50 items. He failed to recognize only 4 items for which his rating had been nonhomogeneous. These data clearly indicate that R.W.'s failures on recognition are not due to any lack of attention.

Yes-No Recognition following a Semantic Orienting Task. To obtain further evidence that an attentional problem at the time of memorization was not the core of R.W.'s recognition difficulties, an experiment was carried out using a more powerful orienting task than that used by Warrington. This was based on the semantic orienting task procedure used by Craik and Tulving (1975). The subject was presented with a series of cards, each containing both a sentence with a word missing and a target word. For each sentence he had to say whether the target would fit well into the sentence. R.W. did this very well. In this test 30 target words occurred once and 30 occurred twice, on each occasion with a different frame sentence. After a 1 min delay, the subject was given 5 min to recall as many target words as possible. He was then presented with all 60 targets together with an equal number of distractors and had to select the words that he had seen before. In this procedure, unlike Warrington's, the subject was not told how many targets to recognize.

On the recognition part of the test, there was virtually no difference between the number of words that R.W. underlined that had been presented (21) and those that had not (19). In other words, his score corrected for guessing (0.05) did not differ from chance. His score was very significantly inferior to that of 10 control subjects for the stimuli presented once, for those presented twice, and for both combined. R.W. produced 4 times as many false positive responses as the mean of the control group—a significantly higher figure. His score (14) for the items presented twice was considerably higher than his score (7) for the items presented once, a pattern which was similar to that of the control subjects.

After he had underlined the 40 words that he thought had been presented, R.W. was told that there were 60 targets and was asked to underline an additional 20. Out of the total 60 responses that he made, 33 were targets and 27 were distractors. Again, his recognition performance did not differ significantly from chance.

Summary. In tests involving recognition of words, faces or paintings, R.W.'s results were abnormal, and are comparable with those of the severely amnesic patients described by Warrington and Weiskrantz (1978). The results are difficult to explain in terms of artefacts such as lack of attention or of motivation, fatigue, or difficulty in following instructions. R.W.'s confidence rating reveals an important pathological factor: his degree of confidence in incorrect responses was very high.

Tasks of recall

Six tests of recall after a single presentation were performed. Three involved lists of words. The first two involved Immediate Free Recall, a task which is classically used in studies of amnesia to distinguish short-term and long-term memory components. The third, known as Final Free Recall, involved a second attempt to recall after all the individual free recall trials had been carried out; this was designed to show whether the patient could recall a relatively large amount of information normally. The fourth was a test of Delayed Free Recall, that is recall after a delay of 30 s involving a filler task; this procedure is assumed to eliminate the short-term memory component. The fifth was the recall version of the Craik and Tulving procedure using a semantic orienting task: together with the recognition test already reported it allowed a direct comparison to be made between recall and recognition. Finally, there was a test of Recall of Short Stories.

Immediate Free Recall of 10 words. The test form used in this study consists of 30 lists of 10 words. Words are nouns and adjectives, of a frequency greater than 30 per million (Juilland *et al.*, 1970). They were assigned to lists at random, with the exception that obvious associations were avoided. The words were spoken by the experimenter at a rate of 1 per 3 s in a neutral voice. The subject had to recall as many words as possible, in any order, without any time pressure. He was instructed at the beginning of the session to try to recall the last few words of the list first of all; this ensured that the recency effect could be considered a relatively pure reflection of primary memory.

On the whole, R.W.'s performance was well within the normal range. On the Free Recall curve it was within the normal range for all serial positions (*see* fig. 2). Tulving and Colotla's (1970) analysis revealed that both his short-term and long-term memory components were well within the normal range (*see* Table 5). The number of confabulations (i.e., words not present in the presented or preceding lists material) and perseverations (i.e., errors corresponding to a word belonging to a previous list) per list, were both at the upper limit of the normal range.

Immediate Free Recall of 15 words. The procedure was exactly the same as in the one described above, except that R.W. was presented with 12 lists of 15 words in each. The number of correct responses that he produced was below the normal range (*see* Table 5). Applying the analysis of Tulving and Colotla (1970), this abnormal result appeared to be due to an abnormal short-term memory component, whereas the long-term memory component was well within the normal range. The number of confabulations produced by R.W. was within the normal range while his number of perseverations was abnormally high.

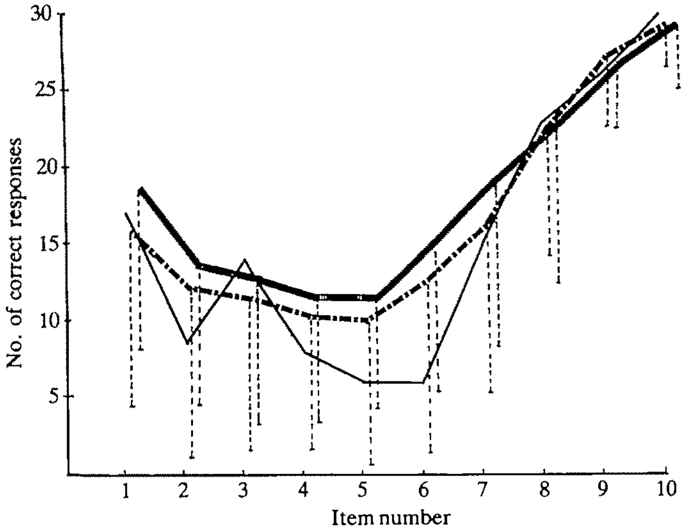

FIG. 2. Test of Immediate Free Recall of 10 words. Serial position curve. The figure represents R.W.'s performance (continuous line) together with the mean and the SD of the 75 control subjects (broken thick line) and those of the 15 control subjects (hatched line) in the same age range as R.W. Broken thin line = 2 SD.

TABLE 5. TESTS OF RECALL[1]

		CR	*STM*	*LTM*	*CONF*	*PERS*
Immediate Free Recall (10 words)	R.W.	5.13	3.23	1.9	0.43	0.5
	75 CS	22-1-51	11-1-63	40-0-35	68-0-7^{L}	60-1-14
	15 CS	6-1-8	2-0-13	6-0-9	14-0-1^{L}	14-1-0^{L}
Immediate Free Recall (15 words)	R.W.	4.42	3.09	1.33	0.58	1
	75 CS	2-1-72*	3-0-72*	12-1-63	63-4-8	74-0-1*
	15 CS	0-0-15*	1-0-14^{L}	5-0-10	10-1-4	15-0-0*
Final Free Recall	R.W.	10			7	2
	75 CS	17-2-56			49-7-19	65-7-3
	15 CS	4-1-10			7-2-6	13-1-1

[1] CR = correct responses; STM and LTM = short-term and long-term memory estimates based on Tulving and Colotla's calculation (1970); CONF = confabulations; PERS = perseverations. The table gives for each test on the first horizontal line, R.W.'s scores; on the second the number of control subjects (CS) out of the 75 having a score less than, equal to and greater than R.W.'s and the probability of being incorrect in accepting that R.W.'s score is abnormal (*$P < 0.06$) or at the limit of the normal range (L); the third line is equivalent to the second except that R.W.'s scores are compared with those of the 15 control subjects of the same age.

Final Free Recall. Following the 12 trials of the Immediate Free Recall of 15 words R.W. was asked to recall, without time pressure, as many as possible of the 180 words which had been presented to him. The number of items correctly recalled was well within the normal range, as was the number of confabulations (*see* Table 5). R.W.'s normal performance on this test is remarkable since it is a highly sensitive test; for instance, young people produce an average of three times as many correct responses as old people

(Delbecq-Derouesné and Beauvois, 1989). It is also a test in which motivation is needed to continue the difficult search for items for which there are few retrieval cues.

Delayed Free Recall. The procedure for this test was the same as that used for Immediate Free Recall, except that at the end of each list there was a filler task lasting 30 s in which the subject counted backwards by threes before attempting recall. The mean number of words correctly retrieved per list by R.W. was 2.8; this was in the normal range of Baddeley and Warrington's (1970) control subjects and much better than those of their amnesic patients. R.W. produced many more confabulations (1.23 vs 0.43 per list) and perseverations (1.2 vs 0.50 per list) in Delayed Free Recall than Immediate Free Recall.

Recall Version of a test using a Semantic Orienting Task. On the Recall Version of the test using a Semantic Orienting Task (*see* Recognition Tasks), R.W. recalled 5 words. His score was within the normal range of the 10 control subjects (4 to 15). However, the number (18) of confabulations that he produced was higher than that produced by any of the control subjects (range 0–12, 12 being an outlier, the others scoring between 0 and 4). In addition, of the 5 words he had correctly recalled, he underlined only 2 at the recognition version of the test (*see above*).

Recall of short stories. R.W. was given 4 short stories to recall. Each story contained approximately 20 items of information. The main purpose of the experiment was to assess whether his performance was affected by providing him with coding cues at the time of memorization and/or by retrieval cues at the time of recall. The 4 stories were therefore used in a 2×2 design. In order to determine whether the presence of coding cues affected his performance, each story was either presented normally or with questions immediately after each new item of information, so as to ensure that he had processed that particular point of the text properly. In the recall situation, he was asked either to recall the story freely or to answer questions about the information in the story. The stories were also presented to 7 control subjects of the same age band and cultural level as R.W.

Three kinds of analysis were performed. First, his overall performance (total number of correct items for the 4 stories) was compared with that of the control subjects. Secondly, the effect of the presence of coding cues and/or retrieval cues on the production of correct responses was assessed. Finally, an error analysis was carried out.

The total number of correct responses produced (31/75) by R.W. was well within the normal range (2 out of the 7 control subjects also scored 31). The effect of the experimental variables on the production of correct responses was the same for R.W. and for the control subjects: for neither the presence of retrieval cues affect performance but for both their performance was significantly improved by the presence of coding cues. However, R.W. produced far more confabulations (29) than the control subjects (range 0 to 6). Certain of those confabulations appeared to result from a confusion between two pieces of information in the stories. For instance, instead of saying that the thieves had been seized with panic 'on hearing the alarm', he said that this was because the police had arrived, an event which occurred later in the story. Other confabulations appeared to result from an ideational association with a piece of information in the story. For instance, instead of saying 'church, school, farm', R.W. said 'church, school, town hall', which is a very common utterance in French.

Summary. The number of R.W.'s correct responses was within the normal range on all but one of the tests of recall (whether they involved lists of single words or short stories). It was perfectly normal on four of them and at the lower limit of the normal range on only two (Semantic Orienting Task and Recall of Short Stories). On some of them (Delayed Free Recall, Recall of Words Using a Semantic Orienting Task and Recall of Short Stories) the number of confabulations was abnormally high. On others (Immediate Free Recall of 10 and 15 words, Final Free Recall) this number was within the normal range.

Recall versus recognition: a statistical analysis

R.W. thus seems to show an interesting dissociation between his recognition performance, which is consistently abnormal, and his recall performance which, on all the tests, falls within the normal range.

TABLE 6. THE NUMERICAL DATA ON THE REGRESSION OF RECOGNITION TESTS OF FACES ON RECALL TESTS[1]

			Regression line			*R.W.'s scores*		
		Correlations	*A*	*B*	*SE*	*Expected*	*Obtained*	*z*
Immediate Free Recall (10 words)	LTM	0.35***	1.65	39.95	4.09	43.08	32	2.71**
	Correct responses	0.35***	1.37	35.4	4.1	42.43	32	2.54**
Immediate Free Recall (15 words)	LTM	0.36***	0.93	40.35	4.08	41.59	32	2.35**
	Correct responses	0.36***	0.90	36.99	4.08	40.97	32	2.20*
Final Free Recall	Correct responses	0.33**	0.11	40.87	4.13	41.97	32	2.41**

[1] The table gives: correlation between each recognition test and each recall test; data concerning the regression line: coefficient A and coefficient B (y = Ax+B) together with the Standard Error (SE); R.W.'s expected and obtained scores; the z value. LTM means = long-term memory estimate based on Tulving and Colotla's calculation (1970); ** = $P < 0.01$; *** = $P < 0.001$. Calculations were carried out considering only one of the recognition scores (32) which corresponds both to the standard administration condition and to the mean of his 3 scores.

TABLE 7. NUMERICAL DATA ON THE REGRESSION OF RECOGNITION TESTS OF PAINTINGS ON RECALL TESTS

			Regression line			*R.W.'s scores*		
		Correlations	*A*	*B*	*SE*	*Expected*	*Obtained*	*z*
Immediate Free Recall (10 words)	LTM	0.38***	1.01	44.41	2.30	46.33	38	3.62**
	Correct responses	0.43***	0.96	40.93	2.24	45.85	38	3.50**
Immediate Free Recall (15 words)	LTM	0.33**	0.48	44.91	2.34	45.54	38	3.22**
	Correct responses	0.41***	0.59	42.35	2.26	44.95	38	3.07**
Final Free Recall	Correct responses	0.33**	0.07	45.07	2.35	45.77	38	3.3**

Explanations as in footnote to Table 6.

Such a pattern of results is so surprising that the reader might doubt its statistical significance. Direct comparisons were therefore carried out between recognition scores and recall scores, whenever they were available on the same control subjects. Those comparisons aimed to establish that R.W.'s scores *cannot* be considered as an extreme position in the bivariate distribution of recall and recognition scores on various tests. Regression lines were calculated for the recognition scores that would be expected for a given score on a particular recall test. Using tests for which data were available on 75 control subjects, Tables 6 and 7 show that R.W.'s recognition scores always lay significantly below the expected value given his recall scores. Figs 3 and 4 illustrate this point clearly.

It might be objected that those dissociations could arise because the two recognition tests involve visual material, whereas the recall tests involve verbal material. Two lines of evidence make this interpretation most implausible. First, a dissociation was also obtained between recall and recognition, when the same verbal material was used. On the Semantic Orienting Test, using 10 control subjects, a regression line was obtained for the recognition score (corrected for guessing) that would be expected for a given level on the recall test (the correlation between the two values is 0.48). The recognition score obtained by R.W. (0.05) lay significantly below the expected value given his recall score ($z = 2.6$; $P < 0.01$). Secondly, his performance on Forced Choice Recognition for words was as impaired as Forced Choice Recognition for faces and paintings.

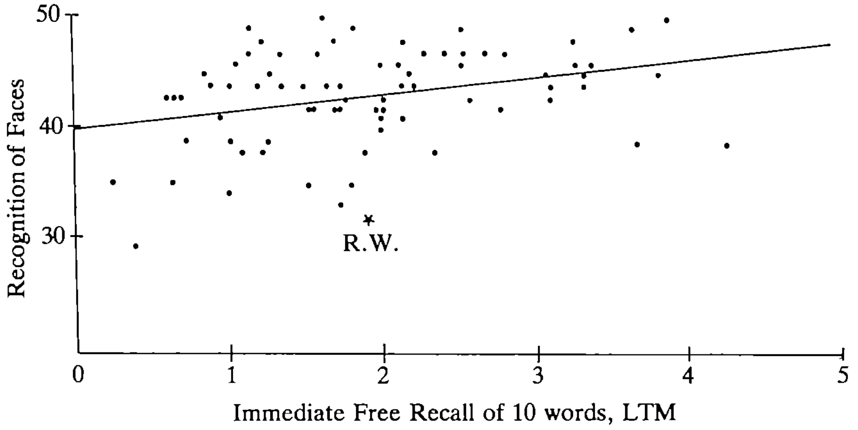

FIG. 3. Regression line of Forced-Choice Recognition of Faces on Immediate Free Recall of 10 words (long-term memory component, LTM).

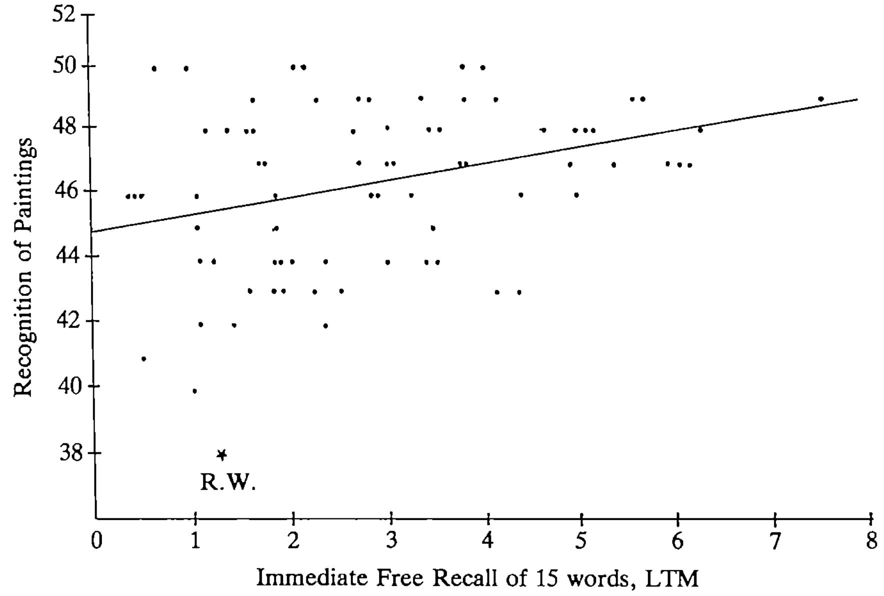

FIG. 4. Regression line of Forced-Choice Recognition of Paintings on Immediate Free Recall of 15 words (long-term memory component, LTM).

Learning

Paired Associates. Clinically speaking, one of the most striking differences between R.W. and amnesic patients was that R.W. performed very well in the Paired Associate subtest of the Wechsler Memory Scale. The decision was therefore taken to investigate how well he would perform on a more difficult task of Paired Associate Learning, one that used only unrelated pairs and words of lower frequency. He was presented with 10 pairs of unrelated words of a frequency of 30 to 41 per million, at a rate of one pair every 5 s. After all 10 pairs had been presented, he was given the stimulus items in the same order with 10 s each allowed for recall of the response words. If he was unable to recall the target or made an error, he was told what the correct response should be. Trials continued until all 10 items had been correctly recalled for 3 successive trials.

R.W. took considerably longer (28 trials) to learn the Paired Associates than any other of the 75 control subjects (range 4–22). If a more lenient criterion was used (i.e., only 1 correct trial), R.W.'s performance (16 trials) was also abnormal (worse than 74 out of the 75 control subjects). He made a mean number of explicit errors (i.e., errors which are not only omissions) per trial (1.78) which is higher than all but 1 of the 75 control subjects (mean: 0.6). In particular, he produced more confabulations per trial (0.53) than any of the 75 control subjects.

Learning with an AB-AC design. The purpose of this group of experiments was to investigate whether the difficulties R.W. had in learning might be due to an abnormal degree of proactive interference. It is well known that amnesic patients have even greater difficulty learning an association when it competes with another (Winocur and Weiskrantz, 1976; Warrington and Weiskrantz, 1978; Winocur and Kinsbourne, 1978). It occurs even when very closely associated words are used so that it is possible for the amnesic patients to learn the initial set of pairs. An AB-AC design was used. In other words, after the initial learning procedure a new set of pairs with competing associations was learned. Apart from the use of words of high frequency, the procedure adopted was the same as in the preceding experiment. As far as learning was concerned (*see* Table 8) the number of trials R.W. required to reach the criterion was normal for AC and at the lower limit of the normal range for AB.

To obtain further information concerning the effect of interference on R.W.'s learning abilities, his performance on the first 3 trials was studied and compared across the 2 different conditions. The mean number of correct responses on the first 3 trials (*see* Table 8) was normal for AB and AC. The difference between his scores on AB and on AC (+1.66) was also in the normal range. The rate of explicit errors per trial made by R.W. was in the normal range for AB and AC. Three kinds of error were distinguished: intralist confusions, confabulations and intrusions (i.e., coming from another list than the one under consideration). R.W. did not produce significantly more confabulations or intrusions (*see* Table 8) than the control subjects.

To summarize, R.W. did not show evidence of an abnormal effect of proactive interference: the difference in the mean number of correct responses on the first 3 trials as well as the number of intrusions did not differ significantly from those of the control subjects.

Repeated Free Recall. The test of Repeated Free Recall can be used both to measure a subject's rate of learning and to assess how much the subject organizes the material in order to learn it. The version used with R.W. involved the memorization of 10 words (frequency 30 to 40 per million; Juilland *et al.*, 1970). On each trial the words were presented at the rate of one every 3 s. Ten trials were used with the same set of words in each, their order being determined by a Latin Square.

On general measures of performance (Table 9), R.W. lay either just outside or at the lower limit of the normal range. By contrast, R.W.'s scores on 4 indices of subjective organization were strictly normal (Table 9). These indices were Bidirectional Pair Frequency (Anderson and Watts, 1969) and the corresponding Adjusted Ratio of Clustering (Pellegrino, 1971), both of which deal with organizational units of size 2; Intertrial Repetition Measure of Organization for units of size 3 (Pellegrino, 1971) and the corresponding Adjusted Ratio of Clustering.

Summary. R.W. was able to achieve a number of learning tasks and in particular to learn new associations, at times normally, even though he had some learning difficulties. These learning difficulties were not due to an inability to organize since he had entirely normal results on the 4 indices of organization. The use of the AB-AC paradigm failed to show any abnormal effect of proactive interference on learning.

Retention of Paired Associates

One of the numerous ways for testing retention is to use relearning. R.W.'s retention of the Paired Associates previously described was tested after a delay of 1 h by repeating exactly the same procedure

TABLE 8. LEARNING WITH AN AB-AC PARADIGM

	No. of trials	*3 first trials*	*Instrusions*	*Confabulations*
AB				
R.W.	9	6.66	–	0.77
75 control subjects	70-1-4^{L}	33-7-35	–	73-0-2*
15 control subjects	15-0-0*	8-0-7	–	14-0-1^{L}
AC				
R.W.	5	5	0.60	0.20
75 control subjects	62-3-10	11-3-61	60-0-15	62-1-12
15 control subjects	14-0-1^{L}	2-1-12	8-0-7	14-0-1^{L}

The table gives: the number of trials to reach the criterion; the mean number of correct responses on the first three trials; the mean number of intrusions per trial; the mean number of confabulations per trial. For each of these measures, their comparisons with the two groups of control subjects are given using the procedure which had been previously described for Tables 4 and 5.

TABLE 9. REPEATED FREE RECALL

	Total no. of correct responses	*No. of correct responses at trial 10*	*BPF*	*ARC 2*	*ITR 3N*	*ARC 3*
R.W.	68	7	7.80	0.29	1.45	0.08
75 control subjects	6-0-69^{L}	1-4-70^{L}	29-0-46	56-3-16	26-0-49	32-3-80
15 control subjects	0-0-15*	0-0-15*	7-0-8	12-0-3	7-0-8	7-0-8

The table gives on the first line R.W.'s scores and their comparisons with the two groups of control subjects using the procedure which has been described previously in Tables 3 and 5. BPF = Bidirectional Pair Frequency; ARC = Adjusted Ratio of Clustering, 2 and 3 units, respectively; ITR 3N = Intertrial Repetition Measure of Organization for units of size 3.

TABLE 10. RETENTION

Proportional decrease	*Paired associates*		
in the number of	*R.W.*	*75 control subjects*	*15 control subjects*
Incorrect trials	0.88	24-3-48	5-1-9
Incorrect pairs on the first trial	0.66	8-3-64	2-1-12
Incorrect pairs on the first three trials	0.76	5-0-70^{L}	2-0-13
Incorrect pairs	0.93	16-0-59	3-0-12

The table gives R.W.'s measures of gain between the scores obtained on the first and second session and their comparisons with the two control groups of normal subjects, using the procedure which has been previously described.

on the same set of words. In order to assess any possible abnormality in R.W.'s relearning, 4 measurements of gain between the scores obtained on the first and the second session were calculated and a comparison was carried out between R.W.'s scores and those of the control subjects (Table 10). The 4 measurements were: (1) percentage decrease in the number of trials required for learning to criteria; (2) percentage decrease in the number of incorrect pairs on trial 1; (3) percentage decrease in the number of incorrect pairs on trials 1, 2 and 3; (4) percentage decrease in the number of incorrect pairs on all trials (i.e., the decrease between the scores obtained on the first and second session, divided by the maximum possible decrease between the two sessions). On these 4 measures R.W. was within the normal range.

DISCUSSION

The interest of this study resides in the description of a relatively pure and totally atypical amnesic syndrome. The amnesic syndrome is pure in the sense that the memory impairment is not associated with any other cognitive disturbances likely to interfere with the study of memory. R.W. is very good on tests of intellectual efficiency such as Progressive Matrices and D48, obtains normal scores on tests of attention, and has only minor abnormalities on tests sensitive to frontal lobes lesions. In addition, his memory disturbance involves mainly the long-term memory component, as all the direct estimates of his short-term memory capacity—different kinds of span, working memory (as measured by two kinds of missing span) and rate of forgetting up to 60 s—are strictly normal. On the other hand, the amnesic syndrome is clearly atypical as on certain tasks he manifests a severe memory impairment while on others he performs well within the normal range. Moreover, the observed pattern of performance is highly consistent over tasks.

R.W.'s pattern of results is mainly characterized by a dissociation between very poor performance on recognition tests strongly contrasting with quantitatively normal results on tests of recall (leaving aside the numerous confabulations). In addition, his performance on learning tests was relatively good and his retention was normal. Finally, R.W. never explicitly showed any sign of awareness of his memory impairment.

Highly abnormal recognition despite normal recall

When R.W.'s long-term memory is tested following the single presentation of a series of items, his recognition scores, which are always abnormal, strongly contrast with his recall scores, which are consistently in the normal range. On all the recognition tests that he had to perform, his scores are much below those of the controls, and this was so whatever the material used (words, faces, abstract paintings) or the experimental manipulations carried out (incidental or voluntary memorization, forced choice or free choice). Where comparisons proved to be feasible, R.W.'s scores are in fact comparable with those of the amnesic patients of Warrington and Weiskrantz (1978). On the other hand, his long-term memory capacity estimated from the number of correct responses was in the normal range (whether it be the long-term component of Free Recall with lists of 10 to 15 words, Free Recall after a delay of 30 s, Final Recall, or recall of more structured elements, such as the information contained in a story). Again, these results are quite different from those usually reported in amnesics, where in severe cases both measures are abnormal (e.g., Warrington and Weiskrantz, 1970) while in milder forms only the recall scores are impaired (Hirst *et al.*, 1986). The contrast between recognition and recall was highlighted directly within one single test, in which the subject was asked to recall, and then to recognize, the words that had been presented; not only was his recall performance normal and his recognition performance abnormal, but out of 5 words correctly recalled, only 2 were then recognized.

In order to be able to interpret this dissociation, it is important to be sure that it is not due to some experimental artefact. Three types of artefact need to be considered.

The first concerns test sensitivity—the recognition tests might be more sensitive than the recall tests, and thus be the only ones that record abnormal performance in cases of slight mnesic deficit. This is implausible since R.W.'s performance is the converse to what is generally observed: recall generally proves more sensitive than recognition, except under highly specific experimental conditions. This is true not only for the effect of mild amnesia but also for the effects of age (Craik, 1977). For instance, the Forced Choice Recognition Test for Abstract Paintings has proved extremely insensitive to age, whereas others are highly sensitive; in Final Free Recall, for example, young subjects produce on average 3 times as many correct responses as old individuals (*see* Delbecq-Derouesné and Beauvois, 1989).

Secondly, the possibility of a statistical artefact has to be considered, namely that R.W.'s performance might represent an extreme position in the bivariate distribution of recall and recognition scores on various tests. Clearly this is not the case: the regression data show that R.W.'s performance scores always lay significantly below the expected value given his recall scores.

Finally, a third kind of experimental artefact must be taken into account. Since the tests were not designed experimentally, it is possible that differences in procedure account for the differences observed on results. Let us, therefore examine the procedure used in the two types of test. In the first place, the recognition tests all orientate attention, which is not the case for most of the recall tests. But orientation of attention generally improves performance, and thus ought to facilitate recognition at the expense of recall. Yet R.W., on the Yes-No Recognition procedure following a semantic orientating task, performs excellently on the orientating task but very badly on the recognition task. In the second place, recognition tests involve the retention of length materials (50 to 60 items), whereas recall tests are often shorter. There are, however, exceptions: the Final Free Recall test involving the retention of 180 items, and the test of recall following a semantic orientating task involving the retention of 60 items; in both of these, R.W.'s recall results are normal. In the third place, the implicit nature of memorization in numerous recognition tests cannot be relevant as when R.W. is explicitly asked to remember, this does not improve his recognition score. Finally, it should be pointed out that, whereas recognition intervenes almost immediately after presentation of the material, there exist two recall tests that involve retention for a certain period of time: Delayed Free Recall and Final Free Recall.

It seems, therefore, that the dissociation observed in R.W.'s performance between impaired recognition and good recall cannot be reduced to experimental artefacts.

Good learning and retention capacities

Even though R.W. sometimes requires more trials than the controls to achieve criterion on certain learning tasks and produces far more confabulations and perseverations, three points are of great interest. First, unlike classical amnesics, he succeeds on several complex learning tasks: he obtains normal scores on the Paired Associates subtest of the Wechsler Memory Scale and on AC of the AB-AC paradigm; his learning of AB is also just below the normal range. This cannot be due to any lack of sensitivity, as tests AB and AC are difficult tasks involving the learning to criterion of 10 pairs of semantically unrelated words; these tests are extremely sensitive to the effect of age (*see* Delbecq-Derouesné and Beauvois, 1989). Secondly, when R.W. obtains abnormal scores in a given learning task, he nonetheless proves capable of succeeding in this task when given more trials than those required by controls. Finally, it was shown that his learning difficulties were due neither to a difficulty in organizing the input, nor to the pathological effect of proactive interference. All of this is far removed from what is usually observed in amnesics. Moreover, R.W. is able to retain what he has learned. The 4 retention measurements carried out on the learning of Paired Associates after a delay of 1 h are normal.

Lack of awareness

R.W. never explicitly showed any sign of awareness of this memory impairment. On recognition tests, where he performed within the range of amnesic subjects, not only did he respond without any hesitations, but he also showed a higher pathological confidence in his incorrect responses since he never admitted to having guessed a single incorrect response. On tests of recall his high rate of confabulations was not associated with any sign of doubt concerning their appropriateness. Moreover, when specifically questioned about his performance on memory tests and about possible memory impairment in everyday life, he always denied having any difficulties (with the exception of his retrograde amnesia).

R.W.'s recognition failure

Which stage of the memorization process is impaired?

R.W.'s dissociation between recall and recognition could be accounted for by a recognition defect located at one of three stages: initial processing of material to be remembered, storage or retrieval.

It seems reasonable to reject the hypothesis of insufficient or inadequate initial processing of the information to be remembered in recognition tests. On these tests, there is clear evidence that R.W. properly attends to the stimulus items, on the one hand (since over three consecutive presentations of the same recognition test, his rating of the stimulus item is highly consistent), and is able to carry out very well a semantic judgement (to decide whether a word would fit into a sentence), on the other.

There are no more grounds to think that R.W. might have suffered from a defect or dysfunction of storage. On the Semantic Orienting Task on which recall and recognition were both tested, he was not told that he would have to remember the presented items, either by recall or by recognition. How could storage be specific for recall on the one hand and for recognition on the other? Therefore, it is unlikely that the impaired recognition performance is due to a storage defect.

One of the major characteristic features of R.W.'s performance is a dissociation between two retrieval procedures; preserved recall versus impaired recognition. The most obvious candidate to account for the behavioural impairment is therefore a recognition defect at the retrieval stage.

Which theory can account for the dissociation between recognition and recall?

Assuming that R.W.'s defect is located at the retrieval stage, how can one account for the dissociation between recognition and recall? Retrieval models can roughly be classified as follows: first, models of retrieval which assume that the recognition/decision mechanism is embedded in the recall mechanism; secondly, models which assume that recognition and recall involve common processes; finally, theories which assume that recognition and recall involve processes which are partly different.

It would not seem possible to account for R.W.'s dissociation between the two kinds of retrieval process on the first class of theories (e.g., Kintsch, 1970; Anderson and Bower, 1972) since these theories would predict that recall cannot be preserved when recognition is impaired.

At first sight, the second class of models would also seem to be unable to account for R.W.'s dissociation. Nevertheless, on one of these theories, the episodic ecphory theory (Tulving, 1983*a, b*), performance can be higher on recall than recognition under certain conditions. According to this model, retrieval depends on the relation between the context at the time of the study and at the time of the test, that is, on the degree to which the cues available at the time of test match the cues during presentation. Recognition is generally higher than recall because these two kinds of cues are more similar in recognition than they are in recall. However, when the context between presentation and test is made more different in recognition and more similar in recall, superiority of recall over recognition can be observed. This result was indeed obtained when stimuli were presented as part of a complex—in paired associates learning—and this was followed either by cued recall or recognition. In the present study, the experimental design was very different: the items to be remembered were presented individually (except for a semantic orienting task); they then had to be retrieved by free recall or recognition. In such an experiment, normal subjects always obtain higher scores on recognition than on recall. R.W.'s dissociation therefore is quite different, under certain conditions, from that shown by normal subjects. It would seem not to be the consequence of a particular experimental situation, but be due to some impairment which needs to be explained in a different way. This class of theories would therefore not seem to be able to account for the results.

The third class of theories, in which recognition and recall involve processes which are partly different, could possibly account for the dissociation observed in R.W. For example, according to two phase models (Atkinson and Juola, 1974; Tiberghien, 1976; Mandler, 1980), recall mainly involves a search process, whereas recognition is largely based on a familiarity judgement which is preconscious, automatic, quick, context free and based on perceptual or intraitem integration (*see*, e.g., Mandler, 1980). An additional, slower and separate process is quite often postulated in recognition (Tiberghien, 1976; Mandler, 1978); it involves the intentional search for contextual information carried out if the familiarity judgement fails to provide an unequivocal decision. According to these theories, R.W. might suffer from a defect in the process which gives rise to a familiarity judgement in recognition whereas the search process involved in recall would be preserved.

Do two phase models account for R. W.'s recognition impairment?

This requires two assumptions: first, that our recognition tests involve mainly a familiarity judgement and R.W. really bases his recognition decision on such a judgement; secondly, that R.W. suffers from some defect of the process involving this familiarity judgement.

Does R. W. base his recognition on a familiarity judgement? A search process would not appear to be of much help to succeed on most of the recognition tests that have been used. Indeed, as far as Forced Choice Recognition Tests are concerned, only a single cue (the context) is available and many items are associated with this same cue, a situation known to be difficult for effective search. Success on these tests would seem therefore to require a sheer familiarity judgement (the Semantic Orienting Task differs in the sense that the subject is provided with contextual information at the learning stage but not at the retrieval stage, and might therefore also try to retrieve some contextual information at the recognition stage). Is the impaired performance of R.W. on recognition tests due to the fact that he does not base his recognition decision on a familiarity judgement, as required by these tests? This does not seem to be so. First, it is known that sheer repetition of the items improves recognition based on a familiarity judgement but does not affect contextual search; but on the recognition test following a semantic orienting task R.W.'s rate of correct hits is much higher (i.e., double) for those items presented twice than for items presented once. Secondly, the level of processing (or the type of encoding) is thought to affect contextual search but not familiarity judgement: R.W.'s recognition performance was as bad when he had been asked to decide whether or not an item was pleasant as when he had been asked to decide whether a particular word was compatible with a sentence. Finally, he does not show any signs of doubt or uncertainty which, for some, is required to set up the search process (Tiberghien, 1976; Mandler, 1980). On the whole, R.W.'s recognition therefore does seem to be based on a familiarity feeling which is required to succeed on these recognition tests. Why then did he fail?

What is impaired in the process involving a familiarity judgement? We may find a hint by considering a difference in the way R.W. performs on two kinds of recognition tests. As we have just seen, on the recognition test following a semantic orienting task the number of correct hits obtained by R.W. is much higher when items are presented *twice* than when they are presented once, which is in accordance with what is expected when recognition has to be based mainly on the familiarity value. However, on Forced

Choice Recognition tests, which we also assume to be based mainly on the use of the familiarity value, his recognition score when items are presented *three times* is no better than when they are presented once. The main difference between the two tests consists of the way in which the response is produced: in the first, R.W. is presented with a single item and has to decide whether or not he has seen it before; in the second he has to compare two items and then decide which one he has seen before. His deficit on those recognition tests which are based mainly on a familiarity judgement might therefore result from an impairment at the stage of the response production or of the decision making rather than from a deficit of the familiarity value itself.

It is obvious, however, that R.W. does not suffer from a general impairment of decision making since, when performing tests which do not involve memory (e.g., D48, Binois and Pichot), he is able to answer quickly and correctly. Might he suffer, then, from a specific difficulty in deciding about information coming from memory, or at least from automatic memory? At the very least, R.W. does not suffer from indecision in recognition tests; he always answers quickly, without any hesitation or self-correction. Also he does not suffer from uncertainty on Forced Choice Recognition tests, when specifically asked; he never admits to having guessed a single incorrect response (whereas he admits his uncertainty for certain correct ones) and is almost always certain to have been right. This indicates first that R.W.'s recognition impairment should not be reduced to insufficient checking of what has been recognized; if this were so, when asked whether he was certain about his response, he would sometimes correct his wrong response, which never happened. Secondly, his behaviour contrasts strongly both with the attitude of normal subjects who sometimes admit that they have guessed, and with the one which is expected from an 'amnesic' patient: R.W. suffers from pathological certainty about his wrong response. He quite often thinks (or at least claims) he has seen something that, in fact, he has not seen, even though he is presented at the same time with what he has really seen before.

Two phase models have some difficulties explaining this behaviour. Indeed, on these models, decision is preconscious and seems to result automatically from the familiarity value of the items. If so, why does R.W. consciously experience such a strong certainty about his wrong answer? If his responses were only the result of a preconscious decision, he should, sometimes at least, experience doubt about his incorrect responses as do normal subjects. Instead, his pathological certainty about his incorrect responses might be the core of his recognition disturbance. R.W. seems, sometimes, to be unable to base his recognition decision upon a distinction between two very different kinds of subjective experience: the one which is aroused by the memorial familiarity value (i.e., 'a feeling of familiarity') and any other which is aroused by the distractor, such as an association. Therefore, it seems likely that R.W.'s recognition responses do not just reflect a preconscious decision based only on the familiarity value of the items. They seem instead to be based on a confusion between two kinds of subjective experience on which he has no possibility of deliberate control as, when reminded for each item of the recognition test that he must respond to the face which he has seen before, and not to something else, he does not succeed any better.

Why is the number of correct responses normal in recall?

In two phase models, response production in recall is conceived to be the result of a search process which is very different from the process based on the familiarity judgement used in recognition. At first sight, therefore, it would appear that R.W.'s impairment in the familiarity process should not affect the search process in recall. It seems possible that his experience of familiarity could intervene in recall without preventing him from producing the correct responses. Indeed, this subjective experience of familiarity might not intervene in the same way as it does in recognition as the search process involved in recall is held to be an active strategic process, whereas the familiarity process, involved in recognition, is thought to be an automatic and more passive one. This active strategic process would seem to be preserved. Therefore, once the selection of the right candidate among all the candidates has been carried out in recall, it can be assumed that R.W. would not be prevented from producing it by the more automatic uncontrolled subjective experience of remembering which could be aroused by a mnesic register other than that of the correct response. On many occasions, he might therefore produce the right answer. It remains possible, however, that a misleading experience of familiarity, or a nonmnestic experience, may be responsible at least in part for the high rate of confabulations that he produces.

Conclusions

To summarize, even though it might seem attractive to base an account of the observed dissociation between poor performance in recognition and good performance in recall on two phase theories of retrieval, they do not provide a good explanation for R.W.'s recognition failure. In order to understand this surprising impairment, we had to take into account a dimension that most of the theories of memory widely ignore, as Tulving (1989) has recently pointed out, that is, the subjective experience of remembering. Following Tulving, we think that the subjective experience of remembering should be clearly distinguished both from the retrieval of stored knowledge *without* the experience of remembering and from memory performance. We further argue that memory performance might sometimes result from an interaction between knowledge retrieved without experience of remembering and the content of the subjective experience of remembering, in a way which is not predicted by traditional theories of memory. Our account of R.W.'s recognition failure is that it does not result from any lack of knowledge, but rather from his inability to distinguish his experience of remembering from another kind of misleading subjective experience triggered by the distractors.

It would be attractive to extend this account, which underlines the possible importance of subjective experience on the performance on recognition tests, to a consideration of the confabulations that R.W. produced in recall: too wide a range of experiences is accepted by him as memories. However, at least 1 patient exists who makes confabulations in recall but has intact forced choice recognition (Kapur and Coughlan, 1980). Further investigations are therefore required to assess whether it is possible that certain confabulations produced by R.W. and the kind of recognition failure he shows result from the same impairment. If this could be shown, then it would provide evidence that misleading subjective experience could also interfere with recall performance.

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APPENDIX 1. LITTLE RED RIDING HOOD

R.W. was asked to tell the story of Little Red Riding Hood (LRRH), which is very well known by everybody in France. He said: 'There was an old granny living in T . . . (the town where the patient lives), who was 85, who was always dressed in red and who was called LRRH.' (Experimenter: 'No, that's not correct'). 'Well, there was a grandmother, a wolf and LRRH. LRRH went to see her grandmother . . . She went through woods and came across a wolf. He ate LRRH, didn't he? No, he almost did . . . LRRH had food for tea in her basket . . . Surely the wolf bolted her tea-things because he didn't eat LRRH. So, LRRH left her basket somewhere while going to her grandmother's. Then, the wolf arrived, he wanted to eat LRRH. But he only bolted what was in the basket . . . Well, that's the whole story. LRRH, very distressed, arrived at the house of her grandmother, who must certainly have cuddled her, if she had been a good granny.' (Experimenter: 'Do you remember anything else?'). 'Since she had been given some food, LRRH may have had to spend a night outdoors . . . She walked and she slept in the woods. Then, she arrived in tears at her grandmother's house. I assume her grandmother cuddled her.'

Later, R.W. was asked 25 rather vague questions about specific points in the tale (e.g., How does it start? What happened then? What did she do? etc.). He answered 19 correctly, which shows that he knew the tale fairly well. For instance, after he had said LRRH told the wolf she was going to visit her grandmother and where she lived, he was asked what happened and then said: 'The wolf rushed to her grandmother's. He took her place, disguised himself as her and waited for LRRH.' When asked what LRRH said to the wolf when she arrived, he replied: 'She expressed surprise about what large ears and large teeth her grandmother had.' In addition to these correct responses, R.W. also produced 5 confabulations, only 1 of which was related to the previous ones: the grandmother gave some money to LRRH asking her to go and do some shopping in the village; the wolf ate what was in the basket; there were apples and oranges in it; the grandmother left the house, leaving her clothes behind; LRRH fled and went back home.

APPENDIX 2. AUTOBIOGRAPHICAL MEMORY

R.W. was questioned about a number of events which had occurred recently in his own life. In particular a long interview about an evening that R.W. had spent with his wife and 3 of their friends 2 days before. Below are listed the details of the events of the evening as they happened, together with the complete transcription of the conversation that took place 2 days later, between R.W. and one of the friends.

Real events

R.W. went out in the late afternoon with his wife and 3 friends of theirs, Robert, Christine and Rose. They first went to the cinema. They then walked along the rue de Lyon. In the street, all of them, except Robert, entered a shoe shop. Some minutes later, R.W. went out and joined Robert to have a drink in a café located in a shopping centre. In the meantime, Rose who had bought shoes in the first shop, went to a second one with Christine. While R.W.'s wife was shopping by herself, Rose and Christine bought two scarves, one red and one white, in the second shop. The 3 women then met up again and went to the café to have a short drink with R.W. and Robert. Unfortunately, the café was closing, so that they could not get a drink. They just sat down with their 3 bags and waited a little until R.W. and Robert had finished their drinks. They then walked through the shopping centre (without entering a shop) before going to a pizzeria to have dinner. Finally, they all had an evening walk on the sea-front.

On the following day, at the patient's house, the patient's wife and Rose tried on the scarves, in his presence. One day later, the patient was asked by one of his friends to describe what had happened 2 days before.

Interview with R.W.

Q.: What happened after the film? R.W.: We went out to dinner . . . that's right; we went out to have a pizza, didn't we? Q.: What happened between the end of the film and the pizza? R.W.: Well, we walked. We went to the 4.30 showing, so we left the cinema around 6.20, 20 to 7. Then we had a walk on the sea-front. And we walked through some shopping parades, a shopping centre. And then, we wandered off gently towards the pizzeria. Q.: Did anyone stop between the cinema and the pizzeria? R.W.: You entered a shop. Q.: What do you mean by 'you'? R.W.: You two (i.e., Rose and Christine) and surely my wife was there too. Q.: All three of us? R.W.: Yes . . . Maybe Robert was there as well. I don't know . Q.: Did you stay by yourself, then? R.W.: Oh I don't know. Robert and I may have stayed outside together. Q.: Try and work it out. R.W.: We went into the shopping parade and there were still a few shops open. And then, of course, you went into the shops. Q.: But who entered the shops? R.W.: I don't know whose idea it was, whether it was Rose's or Christine's. Perhaps it was my wife, she adores that sort of thing. Q.: What about you? Were you alone or with Robert at this time? R.W.: I don't know. He may have entered the shop, too. If Robert was there, I was certainly there too. I didn't remain on my own. But I hate entering shops and buying nothing. Q.: Well, did you or didn't you enter this shop? R.W.: We perhaps entered the shop, yes. Q.: What sort of shop?

R.W.: It was certainly a women's clothes shop. Q.: Are you sure you were there? R.W.: Oh yes, since I had a pizza afterwards!

He then went on to describe what had happened in the shop as if he had been there himself, and furnished several details: 'Scarves were bought by all 3 of the women. We carried 3 bags out of the shop, therefore there were at least 3 scarves. One was blue, another was red and I was struck by the fact that there was no white one'.

He was asked again about this incident about 15 min later; he then said that he remembered having seen the scarves being tried on by his wife and Rose in the shop and that there were only 2, 1 red and 1 white, then he added that he hadn't seen Christine there.

Later, speaking about the drink he had had with Robert, he said that all 5 had had drinks, and described what each of them had drunk. When asked: 'All together? Are you sure?', he answered: 'I don't think that on such occasion we would have been apart.' Then, when it was said: 'Would you be surprised if I told you that we did not have have a drink together?', he replied: 'Oh yes, I am surprised . . . and I regret that it was not the case.' In this confabulation he seemed to mix up what had really happened and what he thought he would have enjoyed.

Analysis of the interview

R.W.'s report contains a number of correct pieces of information associated with confabulations.

The correctly recalled elements are as follows: the timing and duration of the cinema showing; the walk in the town, in particular in the shopping parade and on the sea-front; the visit of the 3 women (at least) to a shop where scarves were bought; the 5 of them together in a café; the fact that the women had 3 bags; that they dined in a pizzeria (R.W. gave numerous details about the meal: what each of them had eaten and drunk, their respective positions at the table, etc.); the fact that he had seen Rose and his wife trying on scarves, but that Christine had not.

Nine confabulations can be found in the transcription of the conversation. The first 6 are clearly confusions: the 5 persons took a walk on the sea-front just after the cinema, before going to the pizzeria (this is a confusion between taking a walk on the sea-front after dinner and having a walk on the rue de Lyon before dinner); Robert may have entered a shop with them (Robert was with them in the cinema, the café and the restaurant, but not in a shop); the women entered a shop in the shopping parade (they walked through the shopping parade but entered a shop in the rue de Lyon); 'If Robert was there, I surely was there too' (Robert and R.W. went to a café together, they didn't go into a shop); R.W. may have entered a women's clothes shop (he, in fact, entered a shoe shop); R.W. had seen the scarves being tried on by his wife and Rose in the shop (in fact he saw them at home, on the following day). Another confabulation might have been due to an intrusion by ideational association: one scarf was blue, another was red and he was struck by the fact that there was no white scarf (this, very likely, is due to the intrusion of the verbal association 'white, red and blue', very common in French since it reminds us of the French flag). Another results from an assumption on the basis of a correct reminiscence: 'There were at least 3 scarves' since 'we carried 3 bags'. The last confabulation is unclear: all 5 had been present at drinks (R.W. had a drink with Robert only, the others arrived later and could not obtain one).

Several of the events that had given rise to confabulations were subsequently remembered correctly. For example, whereas he had first mistakenly stated that the 3 scarves had been bought and they were blue and red, R.W. later recalled that only 2 had been bought and that 1 was white, the other red.

APPENDIX 3. AWARENESS OF THE DISTURBANCE

R.W. never recognized *explicitly* that, at the time he was examined, he might have been suffering from some memory impairment. The following dialogue is a typical example of the kind of responses that he gave, when questioned about it.

Q.: Did you find it difficult to perform these memory tests? R.W.: Not at all. Q.: Don't you think they are more difficult for you than they would have been before your accident? R.W.: No! Really! Before the operation I had no memory at all. I used to run my company with the help of an excellent secretary and her files. Q.: Do you get the impression that you have some troubles that you did not have before your operation? R.W.: Not at all. Q.: Why did you stop working, then? R.W.: For a year and a half I had been thinking that I would return to my job as my memory was improving. But my company was in fact condemned. Q.: But you are still a member of this company. Why don't you take an active part in it? R.W.: Because, just like the other members of this company, I have got an insurance policy which pays me 80% of my salary. Q.: Do you think you would be able to take up your job again if you wanted to? R.W.: Not as the managing director . . . because there is no longer any money in it. Q.: But if you wished, could you do it again? R.W.: Yes, certainly. Without any trouble.

When, later, R.W. was asked why he was still visiting a therapist twice a week, he answered: 'It's a good training. Twice a week I have to make my memory work. Before my operation I had no memory at all. Now I have a good memory. Any friend of mine can tell you that. Such training would be good for anyone'.

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EVIDENCE THAT THE LONG-LATENCY STRETCH RESPONSES OF THE HUMAN WRIST EXTENSOR MUSCLE INVOLVE A TRANSCEREBRAL PATHWAY

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SUMMARY

Ballistic wrist extensor movements were interrupted by a sudden perturbing force in two conditions, and subjects were asked either to compensate for ('oppose') the perturbation or to cease the extensor movement ('let-go') when the interruption occurred. In the first condition, the interruption occurred unexpectedly in some of the trials, whereas in the second it occurred on every trial. Responses were recorded from the flexor and extensor carpi radialis muscles, and from the scalp and cervical spine. Unexpected perturbing forces were associated with an early extensor EMG response (M1) and longer latency EMG responses in both flexor and extensor muscles. When the interruptions occurred in every trial, both the late EMG activity and the cerebral responses were markedly attenuated. The relation between expectation of perturbation and the occurrence or size of the late EMG activity indicates that this response is under supraspinal control. The potentials recorded over the cervical spine and scalp were, like the late EMG activity, influenced by the expectancy of interruption. These potentials persisted even when the potentials related to the mechanically elicited SEP were removed by subtraction of responses to anticipated interruptions from those to unanticipated interruptions. The earliest of these potentials preceded the late EMG activity by 30–50 ms. They were present when the late responses were present, absent when the late responses were absent, and became progressively smaller when the late responses became smaller, suggesting a tight coupling between these events and the late EMG events. These results indicate that cerebral activity, unrelated merely to mechanical stimulation, consistently precedes the late EMG activity, and thereby directly suggests that the long-latency response has a cerebral (possible cortical) pathway.

INTRODUCTION

When a sudden force is applied to a muscle that is either isometrically contracting or in motion, a series of EMG responses can be recorded. The earliest EMG response (M1) is generally agreed to reflect the monosynaptic stretch reflex, but the physiological basis of the following long-latency EMG activity in humans is uncertain. Some authors have attributed it to segmental activity resulting from grouped discharges in group Ia primary afferents (Hagbarth *et al.*, 1980, 1981) or separate discharges in fast and slow conducting afferent fibres following the stretch stimulus (Matthews, 1984), or from

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slowly conducting polysynaptic pathways within the cord (Hultborn and Wigström, 1980). Others, in contrast, have attributed it to activity in a long-loop (possibly transcortical) reflex pathway (*see* Marsden *et al.*, 1983, and Chan, 1983, for reviews). Attempts to provide support for the concept of a long-loop reflex pathway have included studies of the relationship between somatosensory evoked cerebral potentials (SEPs) recorded over the scalp in response to muscle stretch and the various components of the EMG response (Conrad *et al.*, 1984; Abbruzzese *et al.*, 1985). Such studies, unfortunately, provide only indirect evidence of a long-loop process since mechanical somatosensory stimulation may elicit SEPs, regardless of whether any late EMG activity is produced. In order to provide direct evidence for the operation of a long-loop supraspinal reflex arc using evoked cerebral potentials, it is necessary to eliminate, if possible, the contributions of the mechanically elicited SEP to the potentials recorded.

Hammond (1956) initially showed that the amplitude of these late EMG responses was influenced by whether subjects opposed or did not oppose the stretch stimulus. Others have obtained similar results (e.g., Thomas *et al.*, 1977; Lee and Tatton, 1978), suggesting that the late EMG responses are under some degree of voluntary control. Rothwell *et al.* (1980) studied the late EMG responses in three different experimental circumstances in which the predictability by the subject of a sudden perturbing force being applied to a particular muscle was altered. In the first (most predictable), the perturbations occurred randomly 500–650 ms after a warning stimulus, whereas in the third (least predictable) they occurred similarly but only on half of the trials; subjects either had to react or not react (let-go) to the perturbation. They concluded that the increased amplitude of the late EMG activity in the react condition of the first experiment relative to the let-go condition was due to an overlap with voluntary EMG activity, when perturbation was predictable, rather than to a genuine modification of the late EMG response. Their fig. 1 also shows (but this is not commented upon) that late EMG activity in the most predictable let-go condition is less than in the others. This raises the possibility that expectancy of perturbation may influence the late EMG activity.

We have therefore recorded the long-latency stretch reflex together with the SEP following interruption of voluntary movement by a sudden perturbing force in two conditions. In the first, the interruption occurred unexpectedly and in the second the same interruption occurred with every movement. We then subtracted the waveforms obtained in the expected condition from those in the unexpected condition (i.e., conditions using the same mechanical stimulus and presumably resulting in the same mechanically elicited SEP) to determine the relationship, if any, of cerebral events recorded in this manner to the late EMG response.

METHODS

Seventeen right-handed subjects (aged 27–38 yrs; 15 men and 2 women) participated voluntarily in these experiments. Three sets of experiments were performed: 8 subjects participated in the first set, 10 in the second, and 5 in the third.

First set of experiments

Subjects were asked to make a ballistic extensor movement of the right wrist over an arc of 21° against a constant force of 2.3 Newtons (N) to reach a target position. The forearm was fixed and immobilized by strapping it into a metal guide. The movement began with wrist flexed 15° from the neutral position and ended 6° in extension. The force was supplied by a torque motor attached to a handle 3.5 inches from the axis of rotation. Prior to the movement, the handle rested against a stop so there was no initial load on the muscle. Movement of the handle altered the position of a small dot on an oscilloscope screen on which the desired target position was clearly marked. The accuracy of the movement was monitored visually by the subject on each trial. Each subject practised the movement before the experiments to gain familiarity with the task requirements. The movements were self-paced but never more frequent than once every 2 s. Randomly, on 14% of the trials, a step increase in the applied torque occurred 9° into the movement and subjects were asked to compensate for this and still achieve the target position. Each subject was studied in 3 conditions, the order of which varied. The force was increased from the constant background force of 2.3 N to 18.4 N in the first, 13.7 N in the second and 8.0 N in the third condition, respectively.

Cerebral responses were recorded from C3′, C4′, Cz, and P3′ scalp locations (international 10:20 system) and from the neck overlying the spinous process of the second cervical vertebra (CV2), referenced to linked mastoid electrodes. Surface EMG activity was recorded from electrodes placed over the motor points of the right extensor carpi radialis and flexor carpi radialis, each referenced to an inactive electrode placed on the dorsum of the ipsilateral hand, and rectified before being displayed. Position information was recorded directly from a rotary variable differential transformer (RVDT position transducer). Responses to 360 uninterrupted and 60 interrupted movements were recorded for each force level. Responses were recorded over the interval from 180 ms before to 535 ms after the interruption (or when the interruption would have occurred, for the uninterrupted movements) and were averaged separately for the interrupted and uninterrupted movements using a Nicolet Pathfinder II system. The bandpass was 0.3–30 Hz for the cerebral and cervical response. The bandpass for the rectified EMG was 0.16 Hz–3.2 kHz. Position information was unfiltered. Peak latencies were measured by extrapolating lines from the ascending and descending portions of a wave and measuring the latency at the point of intersection. Onset and offset latencies were measured from either the preceding or succeeding peak of opposite polarity respectively or—if there were no such peaks—from the baseline which preceded or followed the wave of interest. EMG activity was also integrated manually over selected periods of time in order to characterize the effect of different experimental conditions on the components of the EMG response.

Second set of experiments

Subjects were asked to make the same ballistic movement described above in four separate conditions, the order of which was varied. In the first and second conditions, the movement was randomly interrupted on 14% of the trials as described above by changing the force from 2.3 N to 18.4 N. Subjects were asked either to compensate for this increased resistance so that they could still reach the target position (intermittent oppose) or cease the extensor movement as soon as the increased resistance was detected (intermittent let-go). In the third and fourth experiments the movement was interrupted in an identical manner, but on every trial. Subjects were then asked either to compensate for (continuous oppose) or relax immediately after (continuous let-go) the interruption. The recording arrangements were as described in the first set of experiments. The rate of self-paced movement was the same in all conditions.

In each of the first two conditions 180 uninterrupted movements and 30 interrupted movements were recorded, and 60 interrupted movements were recorded in each of the last two conditions. Each experiment was repeated 3 times in each subject. Responses in the first, second, and third trials in the 10 subjects were added separately to form 3 separate grand averages. These 3 grand averages were then compared to ensure reproducibility and summed to get the overall grand average.

The speed of the wrist displacement caused by the perturbing stimulus was measured by the slope of the position trace following the onset of wrist flexion. The angular displacement was measured as the amplitude of wrist flexion caused by the perturbing force before either corrective extension or, in the continuous let-go condition, return to baseline.

Third set of experiments

Because of concerns that the afferent discharge may have a long-lasting depressive effect which could attenuate both EMG and cerebral responses, we repeated the experiments performed in the continuous oppose condition described above, but required subjects to have a rest period between each ballistic movement of at least 20 s. In these experiments two sets of 30 interrupted movements were recorded.

RESULTS

Responses to interrupted and uninterrupted movement

Grand average responses for an uninterrupted movement against a constant 2.3 N force are shown in fig. 1A. The rectified EMG from the extensor shows a peak of activity (E1) 10 ms before the onset of movement and a poorly defined peak of activity (E2) towards the end of the movement. The rectified EMG trace from the flexor shows a burst of activity (F1) approximately synchronous with E1 followed by a larger burst of activity (F2) which occurs during the movement 90 ms after E1 and 100 ms before E2. In addition, there is a sustained increase in the level of EMG activity in both the flexors and extensors, most conspicuous in the latter, as subjects achieve and maintain the target position. The approach to the final position caused by these bursts of EMG activity consists of a rapid initial movement (3 radians/s) with a 10% overshoot of the target position, followed by a small biphasic correction. The cerebral responses consist of an initial slow negative shift, the Bereitschaft potential (BP), followed by a positive deflection (P1), both of which are maximal at the vertex and have a slight left-sided emphasis (i.e., they are larger at C3′ than C4′) as described by Shibasaki *et al.* (1980). These waves are followed by a broad, poorly defined positivity which is nonetheless reproducible and largest at the vertex. Over the cervical spine, there is a well-formed negative-positive complex which follows the onset of movement by 120 ms.

The grand average responses to this movement when it is interrupted by an unexpected 18.4 N force (fig. 1B) are different. The initial bursts of activity in the extensor and flexor EMGs (i.e., E1, F1, and F2) are similar to those in the uninterrupted movement, but additional activity occurs in both muscles. In the extensor, approximately 40 ms after the interruption, there is a 'shoulder' on the later, higher amplitude EMG activity that represents the stretch reflex (M1). Later EMG activity begins in both flexor (FM2) and extensor (EM2) approximately 65 ms after the interruption and about 45 ms before the corrective movement. This activity peaks approximately 10 ms earlier in the extensor than flexor and lasts 80–90 ms. In addition, the sustained EMG activity is increased in both extensor and flexor, especially the former. The position trace is unchanged until the interruption, which causes a flexion of the wrist beginning approximately 25 ms after the torque change; 90 ms after this flexion begins, the extension is resumed and, unlike a typical ballistic movement, target position is approached without overshoot but at a progressively decreasing velocity. The early BP and P1 components of the cerebral response are similar for the interrupted and uninterrupted movements, but the succeeding

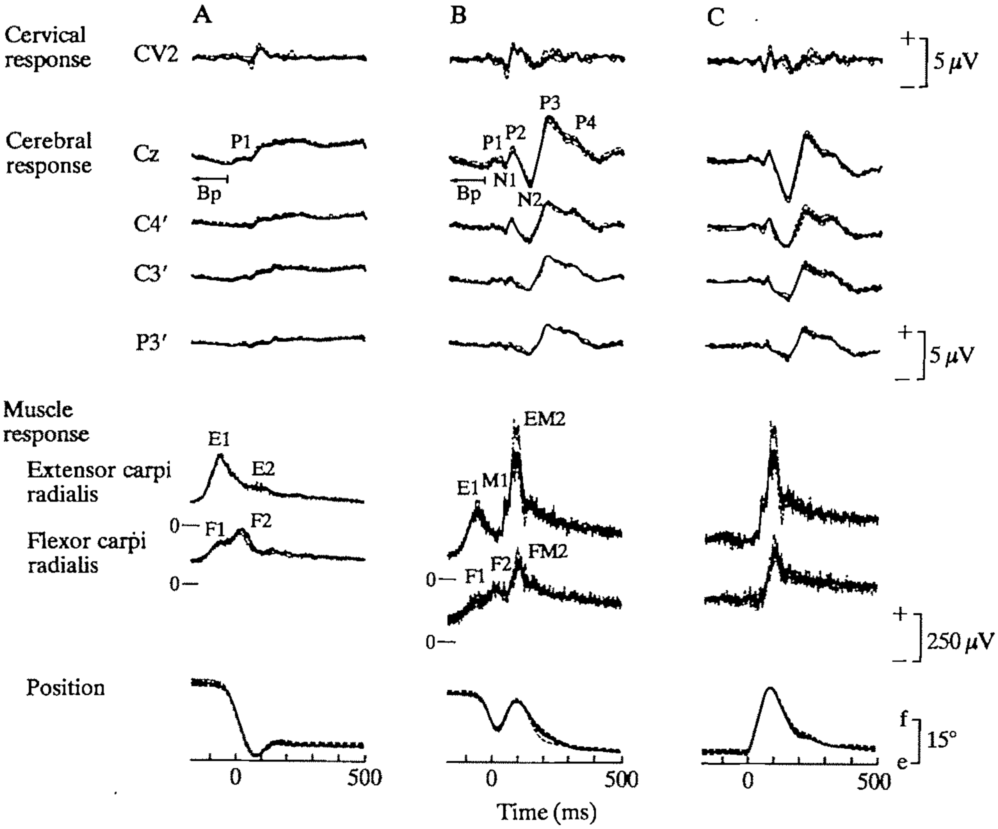

FIG. 1. Grand average responses for the uninterrupted extensor movement against a constant 2.3 N force (A); for the same movement when unexpectedly interrupted by an increase in the constant force from 2.3 N to 18.4 N, for which subjects were required to compensate (B); and the difference waveforms obtained by subtraction of the responses to the uninterrupted movement from the responses to the interrupted movement (C). In this and the succeeding figs, the four panels in each condition show the cervical response (*top*), the cerebral responses (*second*), the rectified EMG responses (*third*), and the position trace (*bottom*). Horizontal bars indicate the zero point for the rectified EMG traces. The calibration of the responses is shown at the bottom right of each panel. The 'f' and 'e' in the position trace calibration indicate flexion and extension, respectively. In each case, 3 preliminary grand averages have been superimposed (dashed lines) and the overall grand average also superimposed (solid line) to demonstrate the reproducibility of the findings (*see* text for details). On the time axis, 0 ms indicates the time when the increased torque was applied (or would have been applied for the uninterrupted movement). Regardless of recording locations (i.e., cervical, cerebral, muscle, and position), the difference in response between the interrupted and uninterrupted movements only occurs after the interruption, as evidenced by the flatness of the initial portion of all the difference waveforms shown in C.

cerebral responses are quite different. There is a conspicuous negative (N1)-positive (P2)-negative (N2)-positive (P3)-positive (P4) complex, maximal at the vertex, which is not present when the movement is uninterrupted (fig. 1). This whole complex is largest at the vertex but with a right-sided emphasis (i.e., larger at C4′ than C3′). In addition, the response recorded over the cervical spine is both larger in amplitude and more complex. No definite component representing the primary afferent volley can be identified in the cervical channel.

Response to perturbations of different force

When the force of the interrupting stimulus is progressively reduced, the amplitude of the late flexor and extensor EMG activity and the cerebral responses is attenuated (fig. 2), without change in latency.

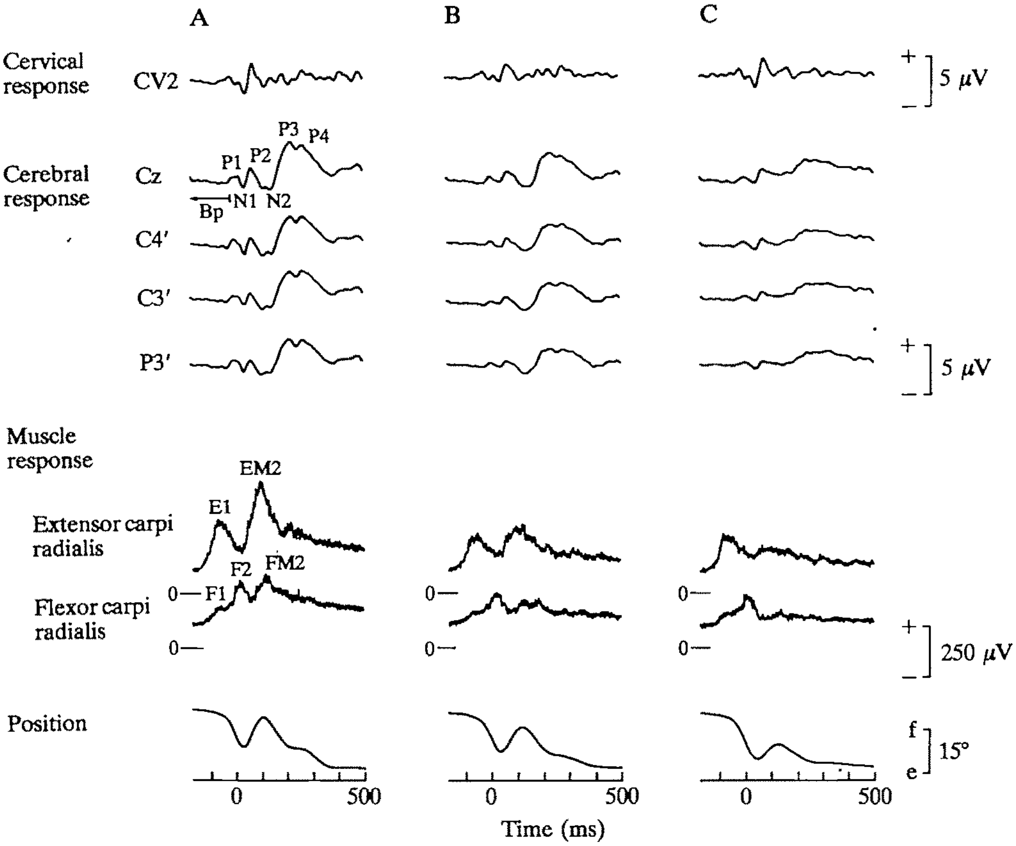

FIG. 2. Grand average responses for an extensor movement against a constant 2.3 N force which was interrupted by an increase in this force to 18.4 N (A), 13.7 N (B), and 8.0 N (C). The display arrangements are as indicated in fig. 1 except that only single grand averages are shown. The size of the cerebral and EMG responses to a perturbing force is seen to depend upon the magnitude of the force. The appearance of the EMG and cerebral responses is slightly different in A than those in fig. 1B because the grand averages are from a different group of subjects.

Effect of required response

When subjects relax (let-go) rather than compensate for the intermittent interruption, the late EMG activity and the cerebral and cervical responses are similar to those recorded when subjects compensate for the perturbation (figs 1, 3, 4) although the sustained EMG activity in flexor and extensor is missing. There are differences between the responses

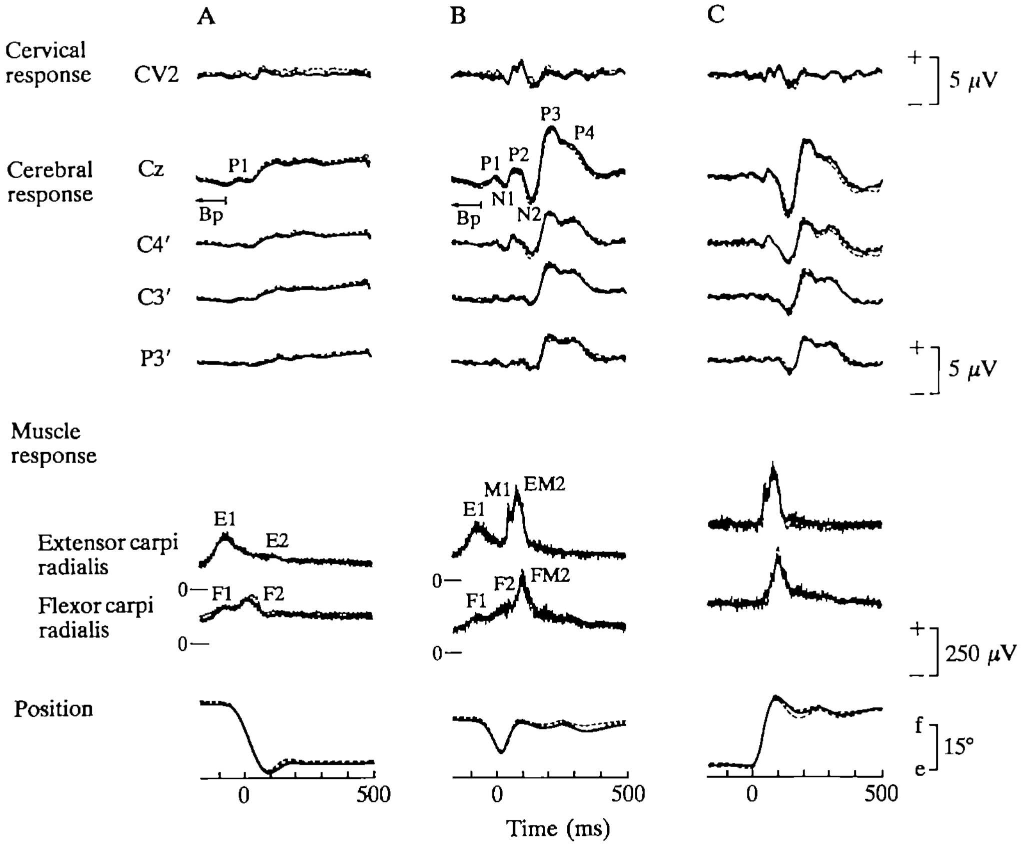

FIG. 3. Grand average responses for the uninterrupted extensor movement against a constant 2.3 N force (A); for the same movement which was unexpectedly interrupted by an increase in the constant force from 2.3 N to 18.4 N, in response to which subjects were required to cease the extensor movement as soon as they detected the torque change (B); and the difference waveforms obtained by subtraction of the responses to the uninterrupted movement from the response to the interrupted movement (C). The display arrangements are as indicated in fig. 1. The cerebral and EMG responses to the perturbing forces are present even though subjects were not required to oppose the movement, but are smaller than when subjects opposed the movement (fig. 1).

recorded in the let-go and oppose conditions. In particular, the M1 response is attenuated in the continuous let-go condition but not in the continuous oppose condition (figs 4, 5). It is, however, present in both the oppose and let-go conditions when the interruption is unanticipated (figs 1, 3, 4). Moreover, the cervical response in the let-go condition is configured differently with a second positive component which is either not present or delayed when subjects oppose the interruption, as can be seen in the difference waveforms shown in fig. 6. It should be noted, however, that the subtracted early cerebral potentials, recorded at Cz, are similar in the oppose and let-go conditions (fig. 6), whereas the late EMG activity is smaller in the let-go condition. Thus the relationship between cerebral activity and late EMG activity may vary with different task requirements.

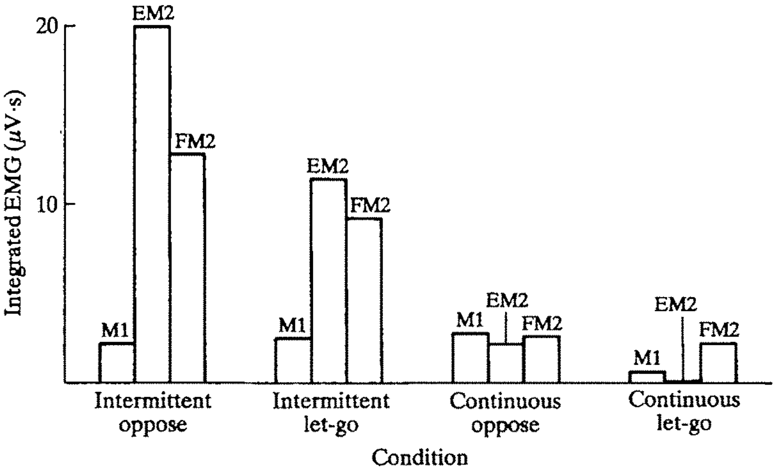

FIG. 4. Difference in integrated EMG activity between the interrupted movement in the 4 conditions (intermittent oppose, intermittent let-go, continuous oppose, and continuous let-go), and the EMG activity recorded when the movement was not interrupted. The EMG activity was integrated from the extensor over the period 40–65 ms following the interruption (M1) and over the period 65–155 ms following the interruption (EM2). The EMG activity from the flexor was integrated only over the period 65–155 ms following the interruption (FM2). The late EMG responses are influenced considerably by the experimental condition in which they are recorded.

Effect of expectancy

When the interruptions are predictable and occur on every trial, the late EMG activity is changed. In the continuous oppose condition, the M1 response is present but FM2/EM2 components are small or absent. In the continuous let-go condition, even the M1 response is missing (fig. 5). When the interval between each ballistic movement was increased in the continuous oppose condition (in the third set of experiments) to more closely approximate the interval between interruptions in the intermittent oppose condition, the late EMG activity was similarly either markedly attenuated or absent (fig. 7). The cortical and cervical responses are also attenuated (fig. 5) in both of these conditions. This is particularly evident in the difference waveform shown in fig. 6, where the responses to the continuous (predictable) interruption have been subtracted from the responses to the intermittent (unpredictable) interruption in both the let-go and oppose conditions. Afferent influences and volitional motor activity will have been largely removed by this subtraction since the stimulus and movement are the same in each condition, and the activity shown is therefore that associated with the context in which the interruption occurs. The late EMG activity similarly depends upon the subject's expectancy of interruption and is preceded by activity recorded over the cervical spine and scalp. Indeed, the earliest such activity (a small amplitude negative wave particularly well seen in the let-go trials) that we recorded was over the scalp beginning approximately 20 ms after the interruption and 40 ms before the late EMG activity (FM2/EM2).

We were concerned that expectancy may have influenced the extent to which the perturbing force displaced the limb. We therefore measured the angular displacement

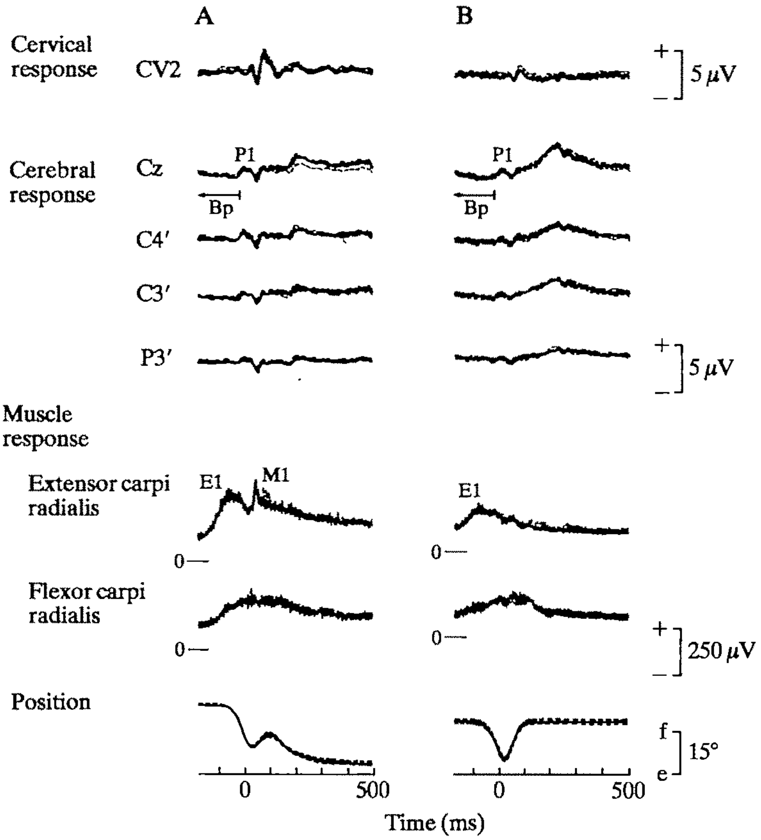

FIG. 5. Grand average waveforms for an extensor movement against a constant 2.3 N force which is interrupted on 100% of the trials by increasing the force to 18.4 N. Responses recorded when subjects were asked to compensate for the increased force (A) and when subjects were asked to cease the extensor movement when they detected the increase force (B) are shown. The display arrangements are as indicated in fig. 1. By comparison with figs 1 and 3, the late EMG activity is considerably attenuated when the interruption occurred predictably, regardless of whether subjects were required to respond by opposing the interruption or not. The M1 response is present in the continuous oppose condition and is absent in the continuous let-go condition.

and speed of displacement produced by the perturbing force under our four different experimental conditions. As can be seen from the Table and fig. 8, we found that in the let-go condition the speed of displacement was the same regardless of whether the interruption occurred predictably or unpredictably, although the angular displacement was greater in the former circumstance. Indeed, in this condition, except for a 4 ms delay in the onset of wrist flexion after a predictable perturbation, there was no difference in the position traces until 90 ms after the torque change (fig. 8). By contrast, in the oppose condition both the speed of displacement and the angular displacement were less when the interruption occurred predictably on every trial rather than unpredictably. Thus the extent to which the limb was displaced by the perturbing force was not influenced in a consistent manner by the expectancy of the subject.

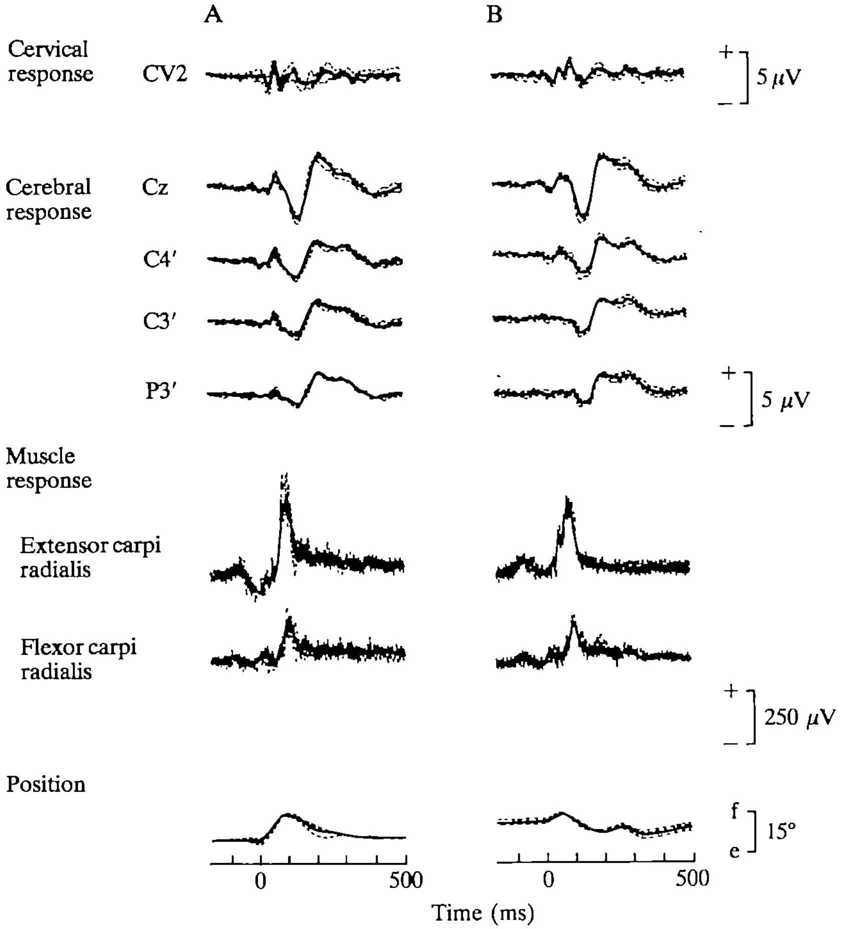

FIG. 6. Grand average difference waveform for both the oppose (A) and let-go (B) conditions. These difference waveforms resulted from the subtraction of the waveforms obtained in the continuous experiments (fig. 5) from those obtained in the respective intermittent experiments in each condition (figs 1, 3). The display arrangements are as indicated in fig. 1. In these difference waveforms, the mechanically elicited SEP has been removed by the subtraction. The remaining activity in the cervical, cerebral and EMG tracings is therefore that associated with the context in which the interruption occurs. This activity begins in the cerebral and cervical tracings 20–50 ms before the onset of late EMG activity.

We were also concerned that differences in the extensor EMG activity preceding movement (E1) may have influenced our results. In the continuous (predictable) oppose condition, E1 was slightly larger and broader than in the unpredictable oppose condition (fig. 8). In the predictable let-go condition, E1 was smaller but of comparable duration to the E1 in the unpredictable let-go condition (fig. 8). Thus in contrast to the late extensor EMG activity (EM2), the early premovement EMG activity did not vary in a consistent manner with the expectancy of interruption. Moreover, these small differences in premovement EMG activity between conditions did not result in any appreciable difference (such as in the speed or onset of wrist movement) in the position traces in any condition before the interruption (fig. 8).

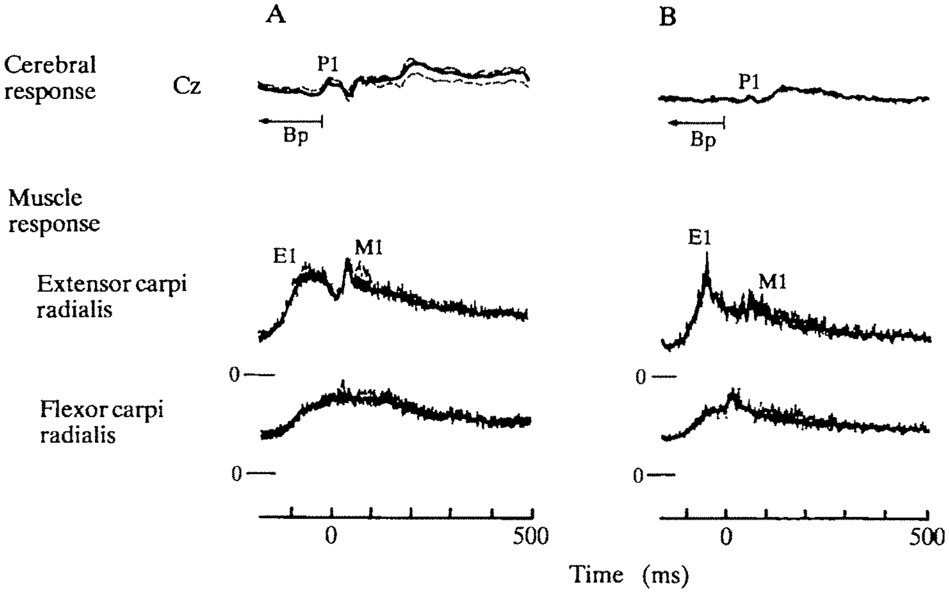

FIG. 7. Grand average waveforms for an extensor movement against a constant 2.3 N force which is interrupted on 100% of the trials by increasing the force to 18.4 N. Responses on the left (A) were recorded when subjects were asked to compensate for the increased force but had only a short rest period between the completion of one movement and the onset of the next. These traces are from those depicted in fig. 5. Responses shown on the right (B) were also recorded when subjects were asked to oppose the interruption but rested for a period of at least 20 s between the completion of one movement and the onset of the next. For simplicity, only the cerebral response at Cz and the muscle responses are depicted. By comparison with figs 1 and 3, and as in fig. 5, the late EMG activity is considerably attenuated when the interruption occurred predictably even when the time between successive movement is prolonged.

TABLE. EXTENT TO WHICH THE PERTURBING FORCE DISPLACES THE LIMB UNDER DIFFERENT EXPERIMENTAL CONDITIONS

Condition	*Angular displacement (deg)*	*Speed of displacement (radians/s)*
Continuous let-go	12	2.3
Continuous oppose	5	1.2
Intermittent let-go	10	2.3
Intermittent oppose	9	1.8

The amplitude of the EMG responses shown in fig. 2 can be compared with each other but cannot be compared directly with those in the other illustrations since the former are from a different group of subjects (*see* Methods).

DISCUSSION

These results indicate that long-latency stretch reflex activity of the extensor carpi radialis can be modified by changing the probability of interruption of a ballistic movement. In addition, cerebral potentials similarly related to the probability of

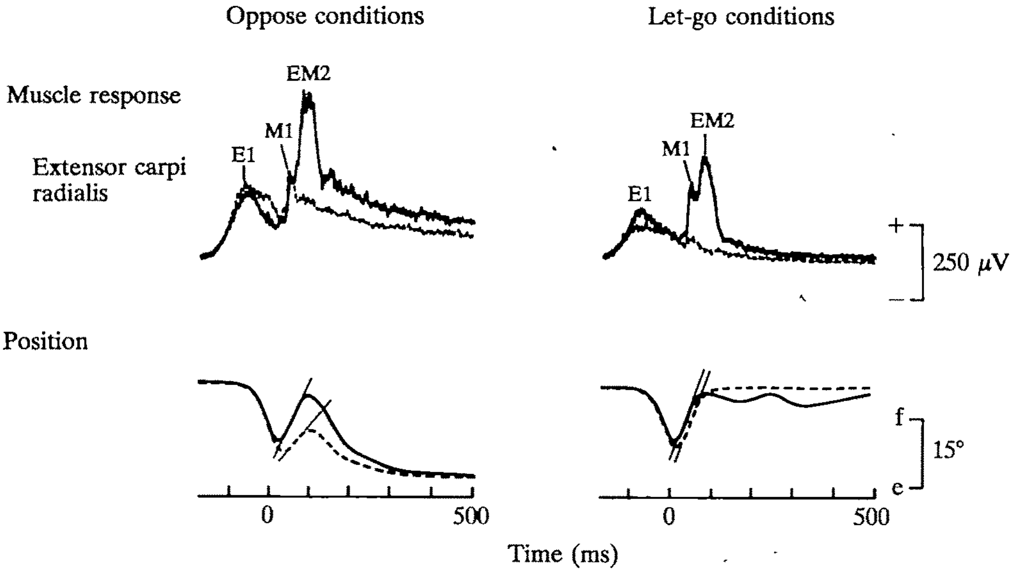

FIG. 8. Extensor EMG responses and position traces in the oppose and let-go conditions. Responses to predictable (dashed lines) and unpredictable (solid lines) interruptions are shown. The position traces are identical until the interruption. In the oppose conditions, when the interruption was predictable rather than unpredictable, there was a delay of 12 ms in the onset of the mechanically-induced wrist flexion as well as a shallower slope following the interruption, indicating a slower speed of muscle stretch. In the let-go conditions, there is a smaller delay (4 ms) in the onset of wrist flexion than in the oppose conditions, and an identical slope following the predictable interruption compared with the unpredictable interruption. The late EMG activity (EM2) is present only when the interruption was unpredictable and is independent of the level of EMG activity preceding the movement or the size of the M1 response.

interruption and both preceding and following the late EMG activity can be recorded from the scalp.

We produced the long-latency response by interrupting a voluntary ballistic movement, rather than by perturbing a muscle held isometrically against a constant force. Marsden *et al.* (1983) also recorded late EMG activity during interrupted movement and concluded that it represented the same events as the activity obtained by perturbing a muscle maintaining a constant isometric contraction. They found that during interrupted movement there was a delay in the onset of late EMG activity in thumb flexors compared with the 40–50 ms onset latency following perturbation of isometrically contracting muscle (Lee *et al.*, 1983), and attributed this to the time taken for the thumb to deviate from its intended path. We similarly found that onset latency of the late EMG activity (65 ms) was delayed, but stretch of the wrist extensors actually began 25 ms after the force change (fig. 3), so that the onset of late EMG activity accorded with that found under isometric conditions. The amplitude of the late EMG activity that we recorded was also similar to that recorded under isometric conditions (Lee and Tatton, 1982) in being dependent upon the force of the perturbing stimulus (fig. 2). Thus we believe that the late activity that we recorded from the wrist extensor muscle represents the late EMG activity recorded by others, despite the different experimental arrangements.

We also found that late EMG activity from the flexor occurred simultaneously with that in the extensor, but others have generally not recorded from both agonist and antagonist muscles.

Rothwell *et al.* (1980) have examined the effect of changes in the predictability of perturbation on late EMG response. As mentioned earlier, they obtained results similar to our own, but did not comment on them. Moreover, in their experiments the interruptions were not as predictable as in our continuous experiments, in which interruption invariably occurred 9° into the movement and approximately 100 ms after the onset of movement.

Others have also recorded SEPs to perturbations, as we did. Conrad *et al.* (1984) recorded cerebral potentials in both let-go and oppose conditions, but comparison with our study is difficult. First, they apparently did not require subjects to maintain a constant resistance against a torque prior to the perturbation, and this may account for the absence of late EMG activity in their let-go condition (Marsden *et al.*, 1976; Hallett *et al.*, 1981). Secondly, their bipolar recording montage used electrodes placed only 6 cm apart on the scalp and this would attenuate any widely distributed potentials (such as those we recorded). Abbruzzese *et al.* (1985) recorded SEPs evoked by wrist stretch using a linked mastoid reference as we did, and obtained potentials of similar configuration and latency (their N1 corresponds to our unlabelled negative deflection preceding P1; our N1 corresponds to their unlabelled negative deflection separating P1 and P2; the remaining components are labelled comparably). However, they did not attempt to separate potentials evoked by the mechanical sensory input from activity that might be more directly involved in a long-loop reflex.

The findings of the present study bear directly upon the physiological basis of the long-latency stretch reflex recorded from the extensors of the wrist. Our results seem inconsistent with a purely segmental origin for this late response and indicate at least some form of supraspinal influence. As shown in our second set of experiments, despite similar stimuli we obtained small and inconsistent late EMG responses when the interruption was anticipated by the subject (fig. 5) and consistent large responses when the interruption was unexpected (figs 1, 3). In other words, a similar afferent input produced a strikingly different late response under different circumstances. It might be argued that, in the oppose trials, the difference in late response was due to the smaller angular displacement and reduced displacement speed in the continuous compared with the intermittent condition (Table). In this view, the smaller late response elicited by the predictable (continuous) interruption with a force of 18.4 N would be similar to the small or absent late response obtained with an unpredictable 8N interruption in the first set of experiments, because in the latter context, as can be seen in fig. 2c, the angular displacement and speed of displacement were comparable with the continuous oppose condition. Three lines of evidence, however, suggest that this is not the case. First, the marked reduction in the size of the late response associated with the 8N interrupting force was accompanied by a similar reduction in the size of the M1 response. In contrast, in the continuous oppose condition there was a conspicuous M1 response (of comparable size to the M1 response obtained in the unpredictable condition), despite the apparent absence of the late responses (fig. 8). Secondly, the amplitude of the late EMG activity was larger in the intermittent oppose condition than in the intermittent let-go condition (figs 4, 8), despite the fact that both the amplitude and speed of muscle stretch were greater in the latter condition (Table). The opposite would be anticipated if either speed or amplitude of stretch were the major determinants of the late EMG activity. Thirdly, and most importantly, in the let-go trials the displacement speed was the same and the angular displacement slightly smaller in the intermittent than in the continuous condition (Table), but the late responses only occurred in the former (figs 3, 5, 6, 8).

In fig. 6, there is an initial upward deflection in the difference waveforms of the position traces, which might be interpreted to reflect an increased displacement speed in both intermittent conditions compared with the continuous conditions. With regard to the let-go conditions, however, the initial upward deflection relates to a slight delay (4 ms) in the onset of the mechanically-induced flexion when the interruption is expected, so that the position trace is offset from, but parallel to, the trace recorded when the perturbation is unexpected. Thus the only difference in afferent input during the first 90 ms after the perturbation in the let-go conditions was this slight delay in wrist flexion, and this would not explain the dramatic reduction in the late EMG activity that we observed in the predictable condition (fig. 8).

It could also be argued that a long-lasting inhibitory effect following the mechanical perturbation, such as that described for the monosynaptic stretch response (Schieppati and Crenna, 1984), may have attenuated both the EMG and cerebral response in the continuous conditions where the interval between successive perturbations was shorter than in the intermittent conditions. Three lines of evidence argue that this is not the case. First, the M1 (monosynaptic) response was not attenuated in the continuous oppose condition when the interval between interrupted movements was short. Secondly, the maximum stimulus rate in these experiments was 0.5/s and the SEP is not generally affected until the stimulus rate exceeds 2–4/s (Pratt *et al.*, 1980; Reisin *et al.*, 1988). Thirdly, and most importantly, the late EMG and cerebral responses were still attenuated in the continuous oppose condition when the interval between interrupted movements was increased to more than 20 s (fig. 7).

Difference in the excitability of the motor neuron pool also seems unlikely to explain our results because the late EMG activity was independent of the level of the premovement extensor EMG activity and the size of the M1 response (fig. 8). This late EMG activity was not only independent of the level of premovement EMG activity but was also independent of the speed and amplitude of muscle stretch, suggesting that differences in afferent input were not responsible for our findings.

It appears that the early M1 response is also under some degree of supraspinal control since it is not present in the continuous let-go condition, and this accords with the findings of others (Lee and Tatton, 1978). However, differences in the supraspinal control of the M1 and later responses are suggested by the pattern of EMG responses recorded under different conditions. Thus in both intermittent let-go and oppose conditions the late EMG activity is greater than the M1 activity (figs 1, 3), whereas in the continuous oppose condition the M1 response is large and the late response is markedly attenuated or absent (fig. 5). Moreover, the late responses are simultaneously present in both flexor and extensor muscles whereas the M1 response is present only in muscles actually stretched by the stimulus. The finding by others that M2 may occur in the absence of M1 (Marsden *et al.*, 1983), and that vibration of stretched muscle inhibits M1 but not the later events (Hendrie and Lee, 1978) also accord with the view that these two responses have a different physiological basis.

The change in M1 response between oppose and let-go conditions presumably relates to descending supraspinal influences on segmental mechanisms and can be rationalized in terms of the need to oppose or not-oppose the interruption. Thus when a subject is asked to oppose an interruption, the M1 response is facilitated and this presumably assists the voluntary opposition. When the subject is asked not to oppose the interruption, the M1 response is inhibited even though the magnitude and speed of the stretch is greater in the let-go condition than in the comparable oppose condition (Table).

The descending supraspinal influence on the later EMG responses could take one of at least two forms. First, it could be the efferent loop of a reflex arc that has a cerebral (possibly cortical) pathway. Secondly, as we suggested above for the M1 response, there could be a tonic influence on a purely segmental mechanism. In this regard, we found cerebral and cervical potentials to be time-locked to the interrupting stimulus, and this would not be expected if supraspinal influences were only exerted tonically on the segmental mechanisms subserving the reflex. Our results suggest that these potentials are related to the supraspinal mechanism controlling the long-latency response, and therefore that there is a long-loop (cerebral) reflex arc. Thus the earliest cervical and cerebral potentials consistently preceded the late EMG response by 20–30 ms and 30–50 ms, respectively, and persisted even when the afferent responses related to the mechanically elicited SEP were removed by our subtraction technique (fig. 6). They were present when the late responses were present (figs 1, 3), absent when the late responses were absent (fig. 5), and became progressively smaller when the late responses became smaller (fig. 2), suggesting a tight coupling between these events and the late EMG events. It is possible, however, that tonic influences may affect this long-loop reflex and this may explain the smaller amount of the late EMG activity in the intermittent let-go compared with the intermittent oppose condition (fig. 4). Thus, for example, if there were a depression of the excitability of the spinal motor neuron pool in the let-go condition (as we previously postulated to explain the reduced M1 response in this condition), the late EMG activity might be diminished despite similar cerebral activity (fig. 6).

The functional significance of the late EMG activity is uncertain, but several authors have suggested that it may be part of a 'servo mechanism' that automatically helps restore a limb to an intended position, although others have challenged this view (*see* Chan, 1983; Lee *et al.*, 1983; Marsden *et al.*, 1983, for reviews). Others have suggested that the late EMG activity is involved in the control of limb stiffness (Houk, 1976; Kwan *et al.*, 1979), and our finding of activity in both agonist and antagonist muscles accords with this, rather than with a servo hypothesis. Presumably such an increase in limb stiffness serves as a brake for the unexpected perturbation, following which corrective limb movements can be activated voluntarily. This might, in part, explain the absence of late EMG activity when the interruption was anticipated and limb stiffness was presumably already adjusted to an appropriate level. The sustained EMG activity in flexors and extensors as subjects achieve and maintain the target position is greater in the unexpected (intermittent oppose) than in the anticipated (continuous oppose) condition (figs 1, 5), perhaps because of a different mental set following an unexpected perturbation.

We also recorded cerebral potentials that were similarly related to expectancy but which followed the onset of late EMG activity by as much as 300–400 ms. The role of this activity is unclear. It probably represents 'event-related' or 'endogenous' activity which has a similar appearance and latency and has been found in comparable circumstances using other forms of sensory stimulation (*see* Goodin, 1986, for review). This late cerebral activity is presumably not related to the sustained EMG activity in the present experiments because, if anything, it is larger in the let-go condition than in the oppose condition (figs 1, 3).

In summary, our results provide support for the existence of a physiologically important supraspinal reflex arc in the generation of the late EMG response in certain forearm muscles of normal humans. It may be argued by some that these responses are not, by their very nature, truly reflex since they are not servo controlled and can be modified by the expectations of the subject. Yet in another sense they are reflex since volition in certain settings cannot prevent them. Similarly, even the earliest EMG response (M1) is not truly reflex since the preconditioning set (i.e., let-go or oppose) can modify it. Perhaps all of these responses lie on a continuum, in the sense of Hughlings Jackson (1958), between absolutely automatic and absolutely volitional behaviour.

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NEURONAL ACTIVITY IN THE HUMAN MEDIAL TEMPORAL LOBE DURING RECOGNITION MEMORY

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SUMMARY

Human medial temporal lobe neuronal activity and event-related potentials were recorded during the following behaviours: contextual recognition of words and faces, semantic discrimination of nonwords from words, and discrimination of stimulus classes based on perceptual attributes. Three distinct classes of behavioural correlates of unit activity were demonstrated by visual inspection of peristimulus histograms and by nonparametric statistics: (1) neuronal excitation during a keypress related to the subject's choice; (2) specific and nonspecific excitation to words; (3) excitation or inhibition to rare stimuli in a sensory discrimination task. Responses specifically to familiar (as opposed to unfamiliar) words or faces, or to tasks requiring recent memory per se were never seen. Keypress excitation was relatively common (32/76 units) and occurred regardless of whether the keypress target was a repeated or nonrepeated word, or the task required recent or remote semantic memory. In a more complex recognition task utilizing two responses and an imperative cue for the patient's response, units with prior keypress excitation failed to generate the response. This suggests that keypress excitation is not strictly tied either to response choice or to generation. The onset latencies and temporal relationship to event-related potentials of the nonspecific and specific excitation to words and the excitation to rare stimuli suggest that they represent contextual encoding of stimuli. Similar evidence suggests that the inhibition to rare stimuli represents inhibitory processes terminating contextual encoding. Thus human medial temporal lobe neurons seem to contribute information during successive stages of a cognitive stimulus-response task: contextual encoding, closure and response-selection.

INTRODUCTION

The human medial temporal lobe (MTL; hippocampal formation, amygdala, parahippocampal gyrus) performs some undefined but critical function in the memory for recent events. Bilateral MTL damage results in permanent anterograde global amnesia (Scoville and Milner, 1957; Squire, 1986). Remote memories, motor skill learning, perception, language, and general cognition are relatively unaffected by MTL lesions. The preservation of memory for skills and action (procedural memory) sharply contrasts with the loss of memory for facts and episodes (declarative memory; Squire, 1986). This dichotomy suggests that during recent memory the MTL interacts with neocortical systems which underlie the extraction of factual information. Essential to defining the

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mechanisms of this interaction is a thorough understanding of the physiological events within the MTL during the encoding, storage and retrieval of a declarative memory trace.

Little is known about human MTL physiology during behaviours requiring memory. Brief reversible disruption of the MTL during the 600 ms following the initial stimulus presentation for encoding or subsequent presentations for recognition testing results in decreased performance. These findings identify a critical latency for the MTL contribution to recognition (Halgren *et al.*, 1985). During this time, event-related potentials (ERPs) are generated by summated currents of synchronously activated, laminated synapses (Wood, 1982; Halgren *et al.*, 1986). These MTL ERPs reflect the general behavioural correlates and temporal activation of large populations of MTL synapses. Two of these MTL ERPs, the N4 and the P3, have been intensively studied. Large MTL N4s are evoked to nonrepeated words or faces, naming of line drawings, and semantically incongruent words at the end of sentences (Kutas and Hillyard, 1980; Halgren and Smith, 1987). These specific behavioural modulators of the MTL N4 waveform suggest that the underlying synaptic currents might represent associated activation of neural networks basic to stimulus integration (Halgren and Smith, 1987). In contrast, the MTL P3 is maximal to repeated words or faces and attended infrequent tones (Smith *et al.*, 1986; Stapleton and Halgren, 1987). This work in conjunction with studies of interictal epileptic spike propagation and local inhibition of single neurons (Altafullah *et al.*, 1986), suggests that the MTL P3 represents active inhibitory processes that are terminating the preceding stimulus processing. Thus during the critical 600 ms immediately following stimulus presentation, MTL synaptic activity occurs which can be used temporally to parse cognitive stages of stimulus processing into associative integration of the stimulus and active termination of the processes.

Complementary insights into the MTL physiology of memory are found in the specific behavioural correlates of local neuronal firing. Despite the behavioural evidence for the role of the MTL in recent memory, few MTL neurons are sensitive to stimulus repetition (Halgren *et al.*, 1978; Heit *et al.*, 1988). In contrast, large numbers of cells within the neuronal populations in the primate inferior temporal cortex (Baylis and Rolls, 1987) and anterior ventral temporal cortex (Miyashita and Chang, 1988) have been found to be sensitive to stimulus repetition. Instead of repetition sensitivity, rat hippocampal neurons have been found to be activated by voluntary motor behaviours (Ranck, 1973) or unique spatial locations (O'Keefe, 1979), suggesting involvement of the hippocampus in movement, or in cognitive mapping (O'Keefe and Nadel, 1978). Primate amygdala neurons display stimulus selectivity and may preferentially fire to individual faces (Perrett *et al.*, 1987). Although human MTL neurons can uniquely code individual words and faces (Heit *et al.*, 1988), it is unknown if they have the full spectrum of animal behavioural correlates of neuronal activation, or additional behavioural correlates unique to humans. Furthermore, the lack of repetition sensitivity of MTL neurons constrains how the MTL may participate in the detection of repetition. The behaviours evoking MTL neuronal activity during recent memory therefore need better definition in order for theories of MTL function to account for the actual information processing transpiring in the MTL.

In order to provide this information about human MTL behavioural neurophysiology, neuronal responses were examined during a time-locked recent memory recognition test for words. Performance on this test depends on the integrity of the MTL; bilateral and left (dominant) MTL lesions severely degrade recognition of repeated words (Milner and Teuber, 1968). Control conditions were included to allow detection of neuronal response to familiarity, stimulus identification and movement.

METHODS

Recording techniques

Complex partial epilepsy unresponsive to medication can be managed with surgical resection of the epileptogenic lesion. Localization of surgical targets often requires depth electrode implantation for direct recording of seizure onsets and patterns of spread (Delgado-Escueta and Walsh, 1983). The subjects in these experiments were 14 epileptic patients with bilateral depth electrodes implanted in some or all of the following MTL sites: anterior, middle and posterior hippocampus, amygdala, presubicular cortex, and anterior, middle or posterior parahippocampal gyrus. In 2 patients the supplementary motor cortex and cingulate cortex were also implanted. The patient population was comprised of 9 males and 5 females, all except 2 were right handed. Electrode placement was confirmed through the direct comparison of postoperative radiographs of the in situ electrodes by reference to the neighbouring ventricles using a stereoencephalographic atlas (Talairach *et al.*, 1958, 1967; Stapleton and Halgren, 1987). Duration of implantation and site selection for each patient were determined by the presenting symptomatology and clinical protocols. Furthermore, to enhance the occurrence of spontaneous seizures for the clinical studies, patients were generally drug free for 2–5 days before these recordings. All subjects gave informed consent prior to the experiments.

Action potentials were recorded from 40 μm blunt wire electrodes (Babb *et al.*, 1973). Simultaneous ERPs were recorded from the same electrode or from one within 5 mm. Only action potentials with a signal-to-noise ratio greater than 2:1 were recorded. The signal from an electrode was initially preamplified with a FET amplifier located close to the patient to reduce movement artefacts, and then split to two recording systems, one for action potentials and the other for simultaneous ERPs. Action potentials were filtered (0.3–3.5 kHz), amplified, and digitized with amplitude-based window discriminators. Because action potentials from hippocampal pyramidal cells can often overlap in amplitude (Fox and Ranck, 1981), and the recordings were from fixed electrodes, the 'units' in this study consisted predominantly of the activity of one neuron, with an occasional spurious action potential from other cells. Up to 8 unit channels with matching ERPs were recorded simultaneously along with an additional 16–24 ERP channels from other sites. The output of the windows, along with trial markers and behavioural data, were collected by a microcomputer for off-line analysis. Action potential data were analysed with sum histograms time-locked to a point 120 ms prestimulus onset. Separate histograms were generated for all correct target and nontarget trials, respectively. Additional (response averaged) histograms were generated time-locked to the actual keypress time for each trial for all correct targets. ERP data were filtered (0.1–100 Hz), amplified, and digitized (200 samples/s) for subsequent off-line averaging by a different computer system (Smith *et al.*, 1986). Raw EEG from MTL sites and scalp (Fz, Cz, Pz, and FPz for EOG), referenced to the nose, was recorded on a polygraph and later examined for artefacts and pathophysiological activity. All trials with epileptiform activity or artefacts were rejected from analysis. Data from any task block with greater than 20% trials rejected for any reason, and units with <0.1 spikes/s were excluded from subsequent analysis. Eighty-nine units were recorded. Of these, a total of 76 recordings were sufficiently free of pathophysiological and electrical artefacts to warrant further analysis.

Behavioural tasks

Behavioural paradigms fall into two categories: testing of recognition memory and sensory discrimination. All patients were tested for recognition memory for words (RM WORD). In this test, 20 common words were presented sequentially on a CRT, and the patient was instructed to memorize each one. Following a brief pause, the same 10 stimuli from the 20 memorized were presented 8 times randomly intermixed with 10 nonrepeating distractor stimuli for 8 blocks of 20 trials. Words were selected for common usage in English. Patients were asked to keypress to the repeated stimulus for each of the 160 recognition trials. To study MTL processing of nonverbal material, in 5 patients the recognition test was repeated with black and white photographs of the faces of white males, chosen for their lack of distinguishing features (RM FACES). In a subset of 4 patients, RM WORD was repeated with a new stimulus set and the subject asked to keypress to the nonrepeated stimuli to control for interactions of stimulus repetition and keypress target designation. Across these patients, the order of task in which the nonrepeating versus repeating words were designated as targets was randomized. Six subjects, following the 160 trials of recognition testing, just watched an additional 100 trials (50 nonrepeating, 50 repeating) and made no overt response, to examine the effects of behavioural response on MTL neuronal discharge. To test MTL responses during remote semantic memory operations, 10 subjects were asked to discriminate sequentially presented words from nonwords (LEXDEC). For all subjects the keypress targets were the words. In order to dissociate response choice from response execution, a variant of the RM WORD task, the delayed cued RM WORD (DCRM WORD) was administered. Three subjects were asked to select their response immediately after stimulus presentation, but to withhold the actual keypress until a cue tone occurred either 700 or 1200 ms after the stimulus offset. For initial training, the subjects, following the cue tone, keypressed either to a stimulus of 4 Xs with their right hand or to 4 Os with their left hand. When the patient had 75–80% correct responses, the task was repeated with a RM WORD stimulus set. Right hand keypress targets were repeated words and left hand targets were nonrepeated words.

In RM WORD, RM FACE and LEXDEC the total trial duration (i.e., stimulus onset to next stimulus onset) was 2500 ms (3000 ms for DCRM WORD). Following a 120 ms prestimulus baseline, stimuli were presented for 300 ms. A 50 ms auditory feedback tone occurred 1200 ms after stimulus onset except for the DCRM WORD where feedback tone occurred 500 ms after either cue tone.

Sensory discrimination tasks were variants of an auditory oddball task known to elicit both scalp and MTL P3 ERPs (Stapleton and Halgren, 1987; Stapleton *et al.*, 1987). Subjects were instructed to count silently to themselves the occurrence of random infrequently occurring (20% of total) high pitch tones embedded in a series of frequent tones of low pitch. Tones were produced for 50 ms every 1400 ms for 125 trials. Subject counts at the end of the task were within 2 of the actual number of target tones. In addition to the basic task, three task variants were used with different subsets of patients. In one variant the subject was instructed to ignore the tones while reading a book during the test. In the second variant, the subject counted omitted stimuli (20% of total) in a train of identical stimuli. The final variant had three stimulus types: infrequent high pitch tones (15% of total); infrequent, unusual, unique, distractor tones (15% of total); and frequent low pitch tones. The subject was instructed to count the high pitch tones. For any task, differences in unit response cannot be state-specific (e.g., due to fatigue or drug intake) because the comparison task conditions are presented over randomly intermixed trials.

Statistical tests

Visual inspection of sum histograms reveals apparent firing differences evoked by task conditions. However, it is conceivable that such differential responses may not be consistent across trials; that is, in some cases these effects could be due to a spurious increase in the discharge rate of the units in only one or a few trials. Therefore, in addition to visual inspection, nonparametric statistics were performed on the data set. The Mann-Whitney U and χ^2 statistics were used to determine if the task conditions *reliably* evoked unit discharges by examining firing on a trial by trial basis (fig. 1). For calculation of the Mann-Whitney U statistic, each trial of a given task was divided into sequential time windows of 120 ms and all the intervals for a given time period rank-ordered according to the number of spikes within that interval (fig. 1). The two tables (one for each task condition being compared) were then used to generate a Mann-Whitney U statistic. Task conditions compared with the statistic were repeated versus nonrepeated words in RM WORDs; repeated versus nonrepeated faces in RM FACEs; word versus nonword in LEXDEC; and infrequent versus frequent tones in auditory discrimination.

It was also of interest to know if the firing-rate changes over the course of a trial from the prestimulus baseline level, regardless of whether that change is significantly different in contrasting task conditions. For example, a unit-response to purely visual characteristics of the stimuli would be identical for both repeated and nonrepeated words in RM WORD, and thus would not be revealed by comparing across task conditions, but would still be of interest. For the investigation of firing-rate changes across the time course of each trial, comparisons were made of prestimulus baseline activity versus sequential 120 ms target or nontarget windows (fig. 1). All results discussed were significant at the 0.01 level with the Mann-Whitney U statistic.

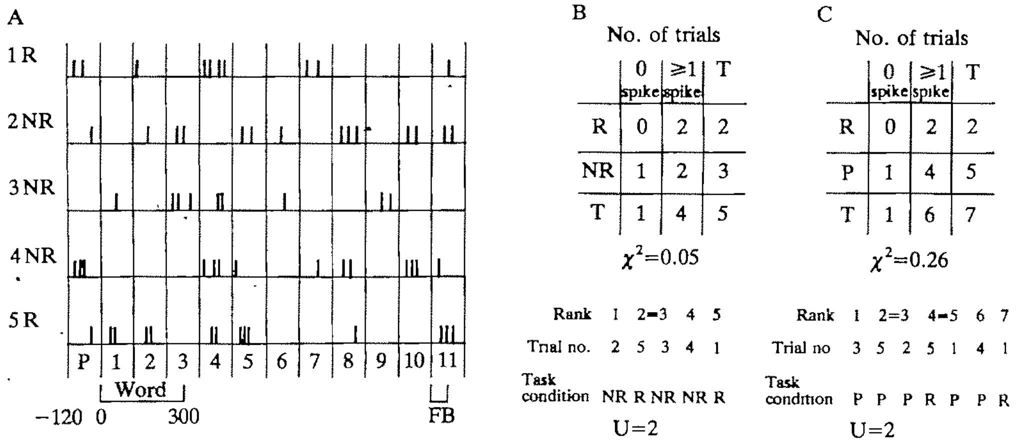

FIG. 1. Schematic representation of the Mann-Whitney and χ^2 statistical analyses as applied to 5 simulated trials. A, 5 trials (1 R, 2 NR, 3 NR, 4 NR, 5 R) divided into 120 ms windows (P–11). Each mark within a window on a trial row represents an action potential from the hypothetical cell under study. In the left column of A, R denotes a repeated and NR a nonrepeated trial. At the lower left hand corner, window P indicates the prestimulus reference window. B, C, 2×2 contingency table used for the calculation of the χ^2 statistic, shown directly below the table. Below the χ^2 value are examples of the Mann-Whitney trial ranking and associated U statistic. B compares repeated (R) versus nonrepeated (NR) trials for time window 4. C represents comparisons of the prestimulus reference activity (P) versus window 4 repeated trials. T = total. FB = feedback tone.

Many of the units fired very slowly, with the majority of single trial 120 ms intervals having only 0 or 1 spike under all task conditions. Therefore, all units were tested with the χ^2 statistic after categorization of the intervals into a 2×2 table of task condition (1 vs 2) by the number of spikes per interval (0 vs ≥1; fig. 1). All responses reported here were found to be consistently significant using both methods. In order to minimize the problem of type II errors due to multiple comparisons, the following critical comparisons were defined a priori: task condition 1 versus task condition 2 in RM WORD in windows 1–6; Mann-Whitney U for units with a firing rate ≥1 spike/s and χ^2 for the other units. The additional comparisons were undertaken in order to confirm and elucidate the nature of the response.

RESULTS

Three behavioural correlates of neural activity emerged from these experiments: (1) excitation related to keypress; (2) excitation to all stimuli in RM WORDs; (3) excitation or inhibition to the infrequent stimuli in the categorization task. Within RM WORDs, no neuronal activation correlates were found for stimulus repetition per se. Furthermore, in comparing the responses of RM WORDs with LEXDEC and other tasks, no clear example of task-specific (e.g., recent episodic vs remote semantic) activation was apparent. Excitation or inhibition did occur to repeated items in RM WORDs and RM FACEs, but never exclusively correlated with stimulus repetition. Similarly, neuronal excitation occurred to words in LEXDEC but again not exclusively to processing of verbal material.

Keypress excitation

Many units (32/76) increased their firing in trials when the patient pressed a key in response to target stimuli. The excitation correlated with key pressing was seen regardless of the nature of the target stimulus, that is, both to repeated and nonrepeated stimulus targets in RM WORD or FACE, and to word targets in LEXDEC. This is in direct contrast to the simultaneously recorded N4/P3 ERP complex, which was modulated by repetition and was not affected by keypress target designation (Smith *et al.*, 1986). Keypress-related responses to target stimuli were not influenced by whether the task was probing recent episodic memory (RM) or remote semantic memory (LEXDEC: fig. 2).

Two predominant temporal relationships of keypress-related activity to the actual keypress were observed: excitatory responses occurring before and those starting after the keypress (fig. 3). Excitation onsets before the keypress (PERIKP) occurred in 15/76 units from the following sites (responsive/total recorded): left amygdala, 0/6 units; left presubiculum, 3/8 units; left anterior hippocampus, 8/31 units; right amygdala, 1/6 units; right anterior hippocampus, 1/14 units; right middle parahippocampal gyrus, 1/7 units; and right presubiculum, 1/4 units. Mean latency from stimulus onset to response onset for all PERIKP responses was 529 ms. On average, the keypress itself followed the onset of these PERIKP responses after 256 ms. These units could be further subdivided on the basis of an apparent bimodally distributed response duration, with 6 of these units (5 located in the left anterior and 1 in the right anterior hippocampus) having the same response onset times before the keypress as the other 9, but with shorter durations of excitation (223 ms vs 538).

The other predominant response-related activity pattern was that following the keypress (POSTKP), seen in a total of 17 units. Like PERIKP response, these were located throughout the MTL: left amygdala, 1/6 units; left anterior hippocampus, 1/31 units; left presubiculum, 2/8 units; right amygdala, 0/6 units; right anterior hippocampus, 8/14 units; right presubiculum, 2/4 units; and right middle parahippocampal gyrus, 3/7 units. POSTKP excitations had mean onsets of 753 ms with average durations of 366 ms. On average, POSTKP onsets followed the keypress after 44 ms.

Although only seen in trials containing keypress target stimuli, these effects have no simple or direct relation to either response selection or execution. Thirteen of the units with clear keypress responses during RM WORDs or RM FACEs were tested with the delayed cued RM WORDs task. In contrast to the well defined keypress responses in

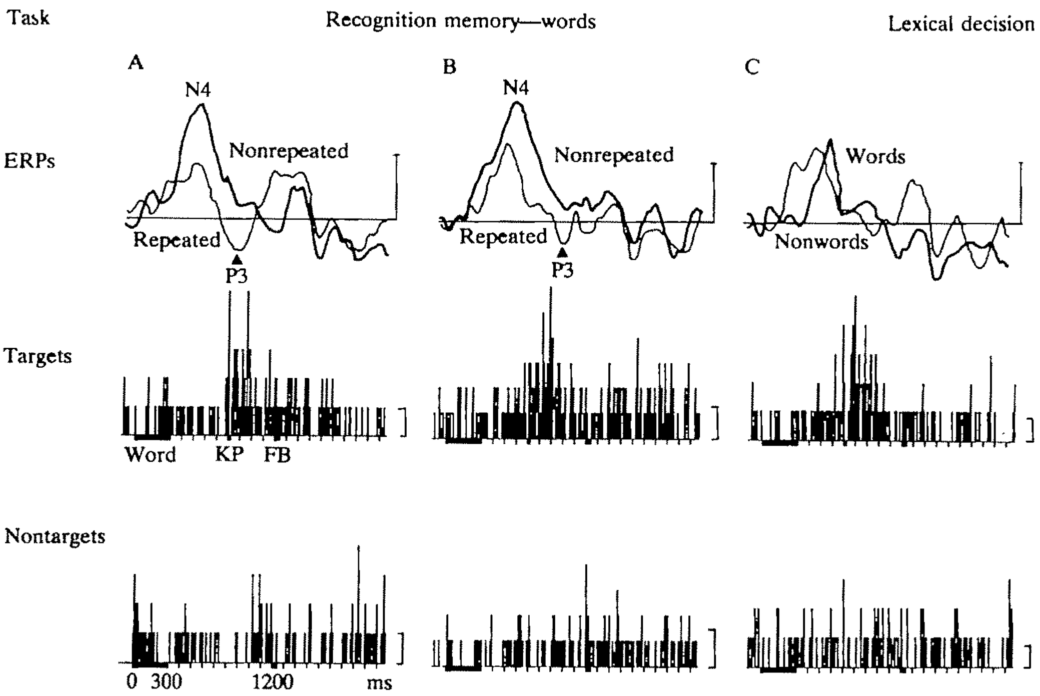

FIG. 2. Keypress related responses of a left anterior hippocampus unit in the RM WORDs task with nonrepeating (A) versus repeating stimulus targets (B), and lexical decision (C). The unit excitation is always to the keypress target and occurs after the subject has responded. In contrast, the simultaneous late positive event-related potential (ERP) is always largest to repeated stimuli regardless of the keypress target. Columns A and B are two separate blocks of the RM WORDs task with repeated or nonrepeating words as keypress targets, respectively. Column C is a lexical decision task with words as the keypress target. *Row 1*: ERP recordings from a cannula electrode in the left amygdala. The ERPs from the left anterior hippocampus were inverted from their normal polarity, probably because the electrode was in or near the generator for the ERP. Thick lines are the ERPs to nonrepeating words (A, B) or to words (C). Thin lines are ERPs to repeating words (A, B) or to nonwords (C). Triangles mark the late positive ERP component that increases with stimulus repetition. Note that the differential ERP effect evoked by stimulation occurs to the repeated target irrespective of that stimulus class being designated as a keypress target. *Row 2*: simultaneous left hippocampal unit responses to target stimuli. The keypress response follows the designated target; press to repeated words (A), press to nonrepeated words (B), and press to words (C). The latency and duration of the response does not alter despite the differences in task conditions. *Row 3*: unit responses to nontarget stimuli; nonrepeated words (A), repeated words (B) and nonwords (C). KP = averaged reaction time; FB = feedback tone. Horizontal scale (B, C) = 100 ms/division. Vertical scale for A = 50 μv, for B and C = 2 spikes/s.

the simple nondelay RM WORDs, none of the units tested was excited or inhibited following the variable cue tone signalling the response execution period. Furthermore, none was activated in the period before the variable cue tone when the subject was formulating his or her response decision (fig. 4).

Relationship of specific stimulus excitation to keypress excitation

Of the 76 units in this study, 39 had been tested in an earlier study (*see* Heit *et al.*, 1988) for selective excitation to one of the repeated stimuli. Of these 39 units, 30 exhibited specific stimulus excitation. This excitation persisted in some units for up to 1200 ms

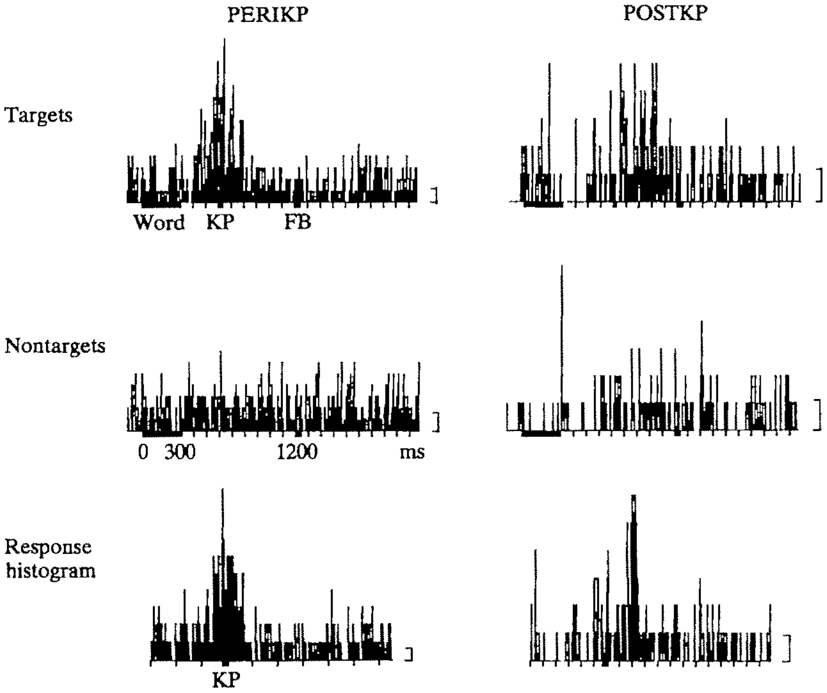

FIG. 3. Excitation beginning before (PERIKP) and after (POSTKP) the subject made his response. *Top* (Targets) *row* shows sum histograms for the response of a left presubiculum unit to repeated (PERIKP) targets and that of a left anterior hippocampus unit to nonrepeated (POSTKP) targets. The *middle* (Nontarget) *row* shows the responses of the same units to nontarget stimuli. In the *bottom row* are response-locked histograms generated from the data displayed in the above sum histograms showing that the PERIKP and POSTKP responses maintain their temporal relationship to keypress in each trial. Abbreviations and scale as in fig. 2.

after stimulus onset, with the most highly focused of the responses occurring primarily in the 300–500 ms latency interval (fig. 5). Although distributed throughout the MTL, the most pronounced specific stimulus excitation was found in the anterior hippocampus, and occurred both to words and faces. Of these 30 units, 11 also showed keypress excitation. Specific stimulus excitation was also exhibited by 6 units of PERIKP responses (located throughout the presubiculum, anterior hippocampus and amygdala) and 5 POSTKP units (in the anterior hippocampus, middle parahippocampal gyrus and presubiculum).

Unequivocal demonstration of specific stimulus excitation requires that the increased response by a unit to a particular word be repeated when that word itself is repeated. Thus, although specific stimulus excitation may occur both to repeated and to nonrepeated words, it can only be detected to repeated words. Eight of the 11 units with specific stimulus excitation and keypress excitation (3 POSTKP, 5 PERIKP) were tested exclusively with repeating stimuli as the keypress target. Therefore, both specific stimulus excitation and keypress-related excitation occurred to the same stimulus class. However, even for these units it was possible to separate these responses on the basis of latency;

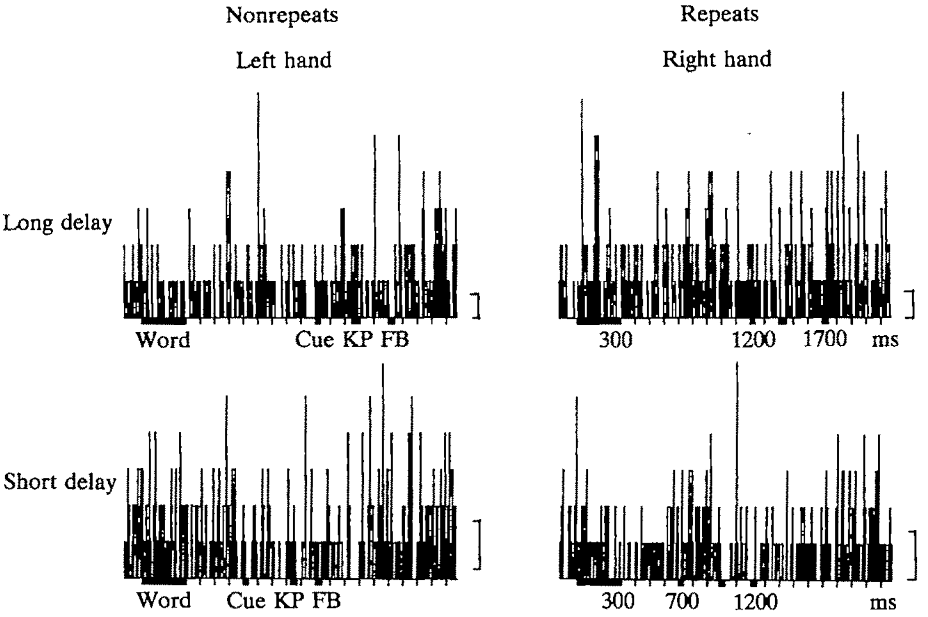

FIG. 4. Lack of keypress excitation during the DCRM WORDs task for a unit in the right anterior hippocampus. This unit has a clear POSTKP response during RM WORDs (*see* fig. 7), but lacks a similar response during DCRM WORDs when the stimulus-to-response mapping is more complex. *Top row*: sum histograms of keypresses following the long delay (1200 ms poststimulus) cue tone. *Bottom row*: histograms of unit responses to short delay (700 ms poststimulus) cue tone. *Left side* column shows responses to correct trials with nonrepeated targets. *Right column* shows responses to correct repeated stimulus targets. Abbreviations and scale as in fig. 2.

specific stimulus excitation always occurred and ended before the keypress response began. The other 3 units with both specific stimulus excitation and keypress excitation were tested during both task conditions (repeated words targets, and nonrepeated words targets). Of these, 2 (1 POSTKP, 1 PERIKP) had selective excitation to one of the *nontarget* repeated stimuli (fig. 6). Thus, the same unit may show specific stimulus excitation or keypress excitation in the same trial at different latencies, or in different trials depending upon the task instructions.

Nonspecific excitation

Seven units were excited, regardless of keypress target designation, to both repeated and nonrepeated stimuli in RM WORDs and RM FACEs, a well as in some instances to words in LEXDEC. Units with this response were located in either anterior hippocampus. Mean onset latency for the excitation to both types of stimuli was 300 ms, with a 561 ms duration. This response type was not seen to infrequent and frequent tones in the sensory discrimination task. None of the units with this response was excited by a reversing chequerboard pattern, suggesting that the nonspecific excitation responses were not due to visual processing. In contrast, 1 unit with a visual sensory response located in the posterior hippocampus, was seen with a short response onset latency (less

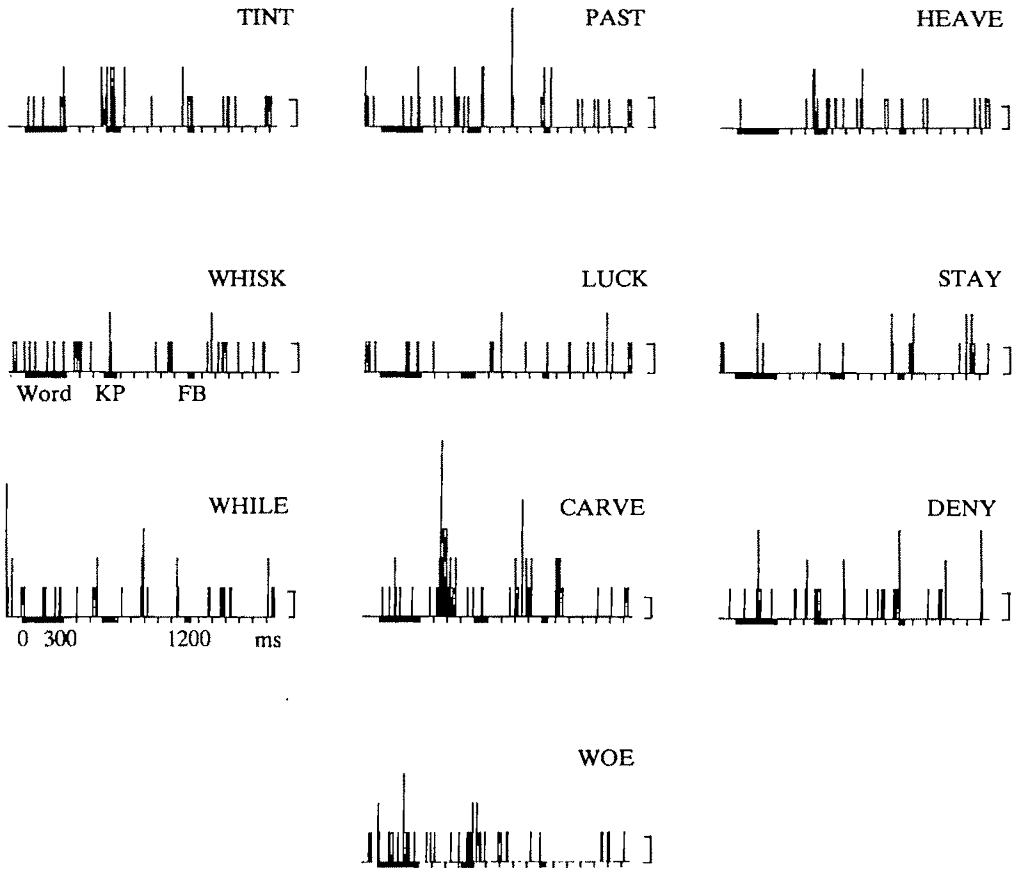

FIG. 5. Specific stimulus excitation in a left anterior hippocampus unit during the RM WORD task. Each histogram is the response of the unit to the 9 presentations of that particular repeated word. The response to CARVE was significantly greater than to any of the other 9 words ($P < 0.0001$). Horizontal scales = 100 ms/division. Vertical scales = 10 spikes/s.

than 50 ms) and duration (<200 ms). This observation is compatible with the findings of Wilson *et al.* (1983, 1984) for visual responses in the human MTL. Of particular interest is the fact that in all 7 units with nonspecific stimulus excitation there was selective excitation to one of the repeated stimuli in the recognition task within the same poststimulus latency as the nonspecific excitation (fig. 7). In contrast, when a unit with nonspecific excitation also had keypress excitation, the keypress excitation always occurred with a later onset latency, as well as occurring in additional (nonrecognition memory) tasks.

Excitation and inhibition to infrequent tonal stimuli

Out of 45 units tested with the sensory discrimination task, 7 responded to the infrequent stimulus tone. Three units, 1 each in the right anterior hippocampus, right middle parahippocampal gyrus and left anterior hippocampus, were inhibited for an average

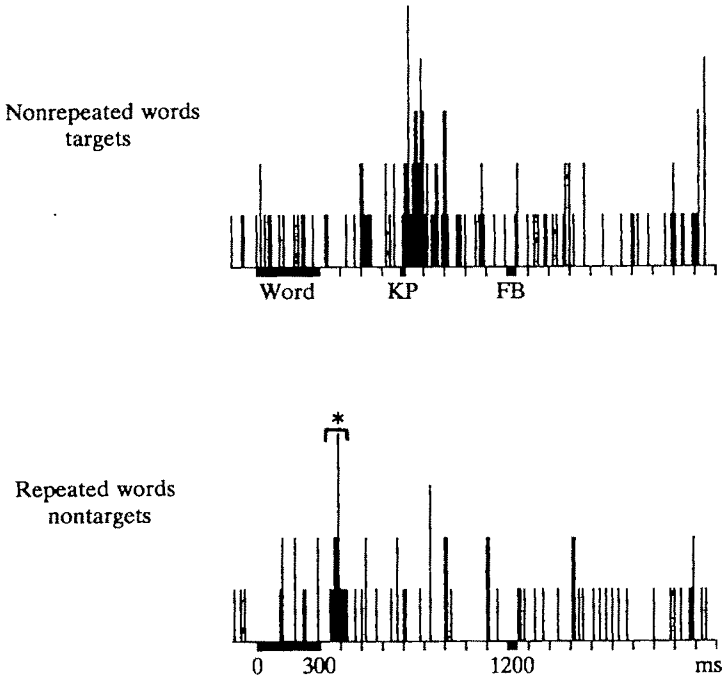

FIG. 6. Disassociation of a keypress response from a specific stimulus excitation to target designation. This unit in the right anterior hippocampus responds to the nonrepeating targets with a clear POSTKP excitation (*top row*). In contrast, its selective response to one repeating stimulus (asterisk) occurs to the repeating nontarget words (*bottom row*). Abbreviations and scale as in fig. 2.

of 375 ms with the inhibition beginning 300 ms after stimulus onset following the infrequent tones (fig. 8). The remaining 4 units, located in the left anterior hippocampus (2) and right amygdala (2) were excited for 75 to 200 ms in the infrequent tones with onsets averaging 125 ms after stimulus onset (fig. 8). In addition to responses during sensory discrimination, 3 of these units had keypress responses and/or specific stimulus excitation during recognition testing. Two of the hippocampus units with infrequent stimulus excitation had POSTKP responses and specific excitation to one of the repeated stimuli during RM WORDs. The middle parahippocampal gyrus 'inhibitory' unit had no keypress related excitation but did have specific excitation to one repeating stimulus.

DISCUSSION

Three types of unit responses occurred in this series of experiments: specific and nonspecific stimulus excitation during recognition memory; excitation related to keypress; and excitation or inhibition evoked by the infrequent tones in the auditory oddball sensory discrimination task. In general, this confirms and extends the observations by Halgren *et al.* (1978) of both stimulus and response related units in the human MTL during memory tasks, analogous to those previously described in animals (*see* Introduction).

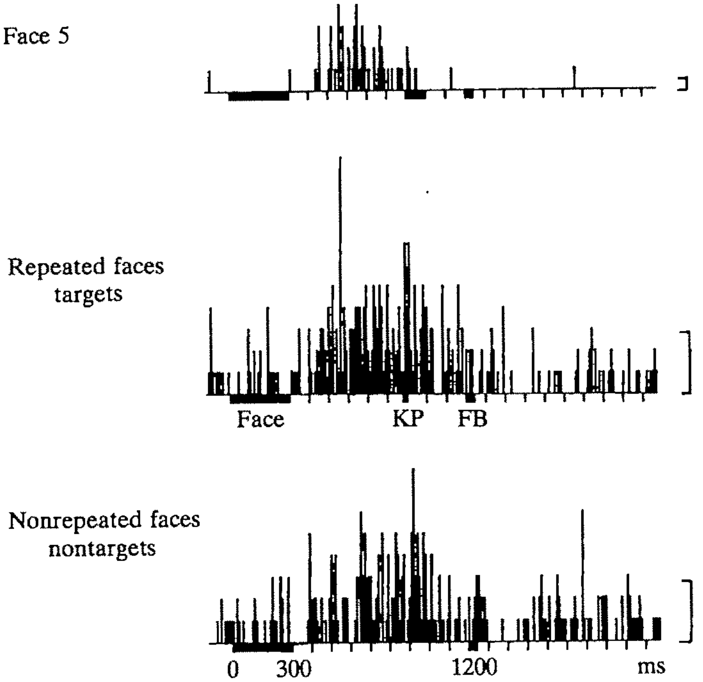

FIG. 7. Nonspecific excitation during RM FACEs in a left anterior hippocampus unit. The *top* sum histogram is the specific stimulus response of the unit to the fifth face stimulus from the 10 repeated presentations in the face stimulus set. The *middle* and *bottom* histograms are the responses of the unit to all repeated and nonrepeated face stimuli, respectively. Horizontal scales = 100 ms/division; vertical scale = 5 spikes/s.

Clinical and experimental evidence implicates the MTL as a critical structure for recent memory in humans (Squire, 1986). Given these observations, it would be assumed that detection of the prior occurrence of a stimulus is the critical role any structure so involved would play. Yet in this, and in previous studies, MTL neurons have not been shown to code stimulus repetition per se. In the earlier Halgren *et al.* (1978) study, the input and output trials of a delayed match-to-sample task were separated by simultaneous match-to-sample trials. Again, MTL units showed no firing-rate changes specific to the memory condition. Identical findings were also obtained in studies of rat hippocampal units during tasks requiring or not requiring memory (Ranck, 1973; O'Keefe and Nadel, 1978). Nonetheless, a few human MTL neurons were found by Halgren *et al.* (1978) to fire when the patient was making a specific effort to recall. In contrast, Ojemann *et al.* (1988) reported human lateral temporal neocortex units that fire specifically during a memory recall task. Additionally, the previously cited primate studies in the inferior temporal cortex (Bayliss and Rolls, 1987) and anterior ventral temporal cortex (Miyashita and Chang, 1988) suggest that detection of stimulus repetition per se occurs in regions afferent or efferent to the MTL. Perhaps the contribution of the MTL to recent memory involves not the detection of repetition as such, but the reconstruction of a contextually

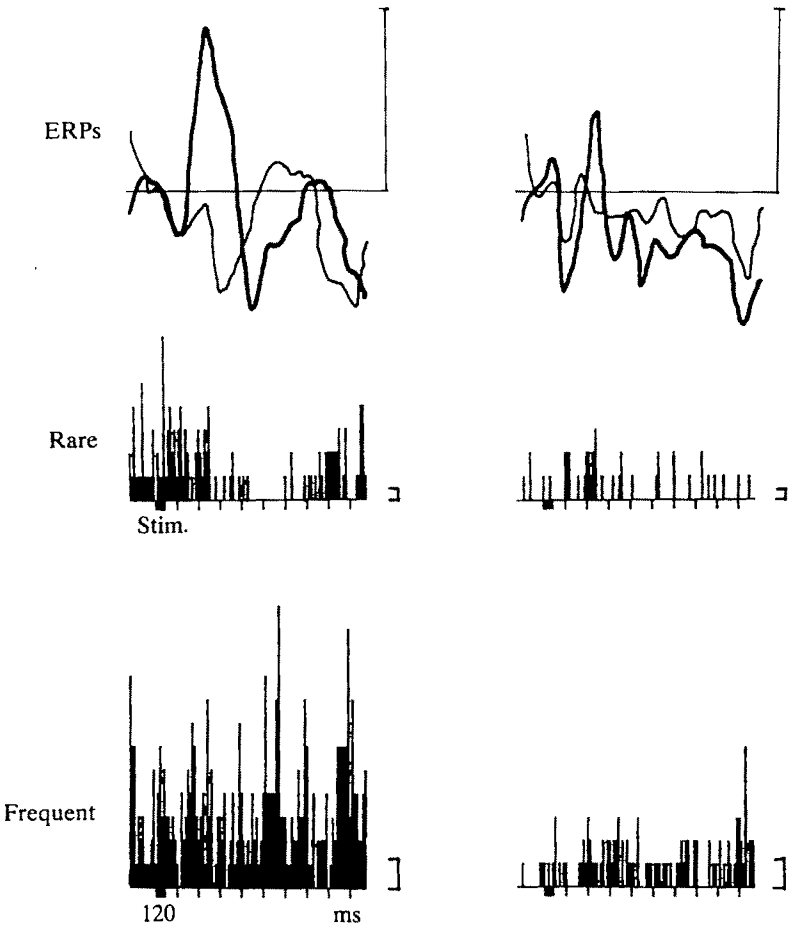

FIG. 8. A late inhibitory (*left column*) and early excitatory (*right column*) unit response to the infrequent tones in the auditory oddball sensory discrimination task. *Top row*: simultaneous ERPs recorded from a neighbouring cannula electrode. Thick line represents ERPs to infrequently occurring tone stimuli, thin line to the frequently occurring stimuli. *Middle row*: unit responses to the infrequent tone. The unit on the left is inhibited, compared with its response to the frequent stimuli, and to the prestimulus baseline (both $P < 0.01$). The histogram on the right shows an earlier excitatory response ($P < 0.01$) to the infrequent tone. *Bottom rows*: nonsignificant unit responses to the frequently occurring stimuli. Abbreviations and scale as in fig. 2. Stim. = stimulus.

based stimulus gestalt, which in turn leads to the detection of repetition through interactions with other structures (Halgren, 1984).

Experimental psychological evidence in normal subjects suggests how a contextually based stimulus gestalt may enhance detection of stimulus repetition. These studies indicate that recognition performance relies on two distinct sources of information: 'perceptual fluency'—the ease of lexical access due to recent exposure, regardless of context; and 'contextual retrieval'—the reconstruction of a previously experienced stimulus-in-context gestalt, given only the stimulus (Mandler, 1980). The contextual retrieval contribution to recognition tends to be maximal after a single stimulus/context presentation, whereas the perceptual fluency contribution develops gradually. Various data suggest that MTL lesions disrupt contextual retrieval, while leaving perceptual fluency relatively intact (Halgren and Smith, 1987). For example, surgical removal of the left MTL and surrounding structures as treatment for epilepsy has been shown to result in decreased episodic recognition in the RM task for words presented only once previously (Smith and Halgren, 1989), although recognition accuracy increased normally as the words were repeated additional times.

Primate studies have also failed to reveal hippocampal firing-rate changes with episodic repetition. However, such changes *were* observed in the inferior temporal cortex (Wilson *et al.*, 1988). These authors have interpreted these data as indicating that it is the inferior, rather than the medial temporal lobe that is essential for recent episodic memory. In contrast, we find the evidence for hippocampal involvement derived from lesions to be convincing (e.g., Zola-Morgan *et al.*, 1986) and suggest that whereas gross repetition-induced firing changes might be expected in neurons subserving perceptual fluency, stable neuronal activity patterns differentiating particular stimuli within a particular context are essential for contextual retrieval. Such patterns occur in the MTL (specific stimulus excitation) at the onset of the N4 divergence to repeated versus nonrepeating stimuli (Heit *et al.*, 1988). Thus instead of providing a gross signal of stimulus repetition, MTL firing patterns may contribute to the reactivation of neocortical circuits encoding a particular stimulus-context gestalt (i.e., contextual retrieval).

In order to clarify how the various MTL firing-rate changes might contribute to recognition memory, it is useful to compare their timing and behavioural correlates with those of simultaneously recorded event-related potentials (ERPs). Summated MTL synaptic currents result in two major ERP components during recognition memory (Smith *et al.*, 1986). The behavioural correlates of the first ERP component, the N4, and its timing (peaking at 460 ms), suggest that it reflects the construction of a cognitive gestalt that encodes the stimulus and its prior contextual occurrences through associative activation of a neocortical/MTL network (Halgren, 1984; Halgren and Smith, 1987). Both the neocortical and the MTL N4 decrease in amplitude and duration with stimulus repetition (Smith *et al.*, 1986), suggesting that some MTL synaptic elements *are* sensitive to stimulus repetition (*see* Halgren and Smith, 1987). Furthermore, the neocortical N4 loses its repetition sensitivity after left anterior temporal lobectomy (Smith and Halgren, 1988). Following the N4, a positive ERP (the P3) occurs that peaks at 620 ms and increases in size with stimulus repetition, and apparently reflects closure of the completed encoding/integration processes. Like the N4, the repetition sensitivity of the neocortical P3 in the recognition task is decreased or abolished by left anterior temporal lobectomy (Smith and Halgren, 1988). The P3 ERP is also evoked in the MTL to the infrequent stimuli during sensory discrimination tasks, although with an earlier peak amplitude (Halgren *et al.*, 1980; Stapleton and Halgren, 1987). Performance on the oddball task, as well as the associated P3, is not altered by unilateral anterior temporal lobectomy (Stapleton *et al.*, 1987). Thus the effects of MTL lesions on both the neocortical ERPs and on behavioural performance indicate that MTL unit activity might be used during tasks that require recent contextual memory, but not for lexical decision or sensory discrimination tasks, even though MTL unit responses have been observed in all of them.

Of the unit activity described in this study, only nonspecific excitation and specific stimulus excitation occur in the appropriate time window, as defined by reaction time and by the MTL N4, for an MTL contribution to encoding. 'Nonspecific' excitation refers to the excitation which was present and approximately equal to repeated as compared with nonrepeated stimuli. To the repeated stimuli the nonspecific excitation was always found to be more or less confined to a particular word, whereas the excitation evoked by nonrepeated words was distributed among many such stimuli. Other units, with specific stimulus excitation, were found to respond to one particular repeating word, in the absence of a response to nonrepeating words. Thus the nonspecific and the specific stimulus excitations have similar latencies and task correlates, but vary in the degree to which specific firing is confined to one particular stimulus, and thus may potentially represent successive steps in the encoding of a particular stimulus/context.

The current results also confirm and extend the report of Halgren *et al.* (1980, 1983) of excitatory and inhibitory neuronal responses in the human MTL to infrequent tones in the auditory oddball discrimination task. The early excitation to infrequent stimuli occurs within the time frame of the N2 ERP, thought to represent stimulus encoding appropriate for the simple auditory discrimination in the MTL (Stapleton and Halgren, 1987). This would suggest that the early excitation to infrequent tones is a variant on the specific stimulus excitation contribution to encoding. However, due to the lack of intrastimulus class distinctions (infrequent tones are all identical, in contrast to the 10 unique repeating words of RM WORDs) no stimulus specific firing is possible, and the activity occurs at a shorter latency.

Indirect evidence suggests that the synapses underlying the MTL P3 are inhibitory in nature and thus termination of encoding and contextual integration would be an active process (Halgren *et al.*, 1983; Altafullah *et al.*, 1986). The inhibition of unit discharges to infrequent stimuli reported here offers further support for P3 representing inhibitory synaptic processes terminating encoding operations within the MTL. However, in contrast to the auditory oddball discrimination task, we observed few inhibitory unit responses during the P3 in the recognition memory task. This apparent discrepancy might be explained by supposing that closure is expressed in this more complex task as a suppression of neuronal firing back to background levels from an elevated state, as opposed to a simple inhibition from a less activated background in auditory oddball discrimination. In other words, during the recognition memory tasks the divergent associative synaptic activation reflected in N4 may persist, and thus mask the inhibition represented by P3.

Following the associative activation processes underlying contextual retrieval is the final firing-correlate identified in this study, keypress excitation. This occurs independently of the primary task condition (i.e., recognition memory versus word/nonword discrimination) and appears to be related to the designation of a stimulus as a keypress target. The keypress excitation is dissociated from specific stimulus excitation by its longer latency and lack of specificity, that is, there was no overlap in the latencies of these two types of cell-firing, even though they both occurred to the same stimuli in the same task condition and were produced by the same units. Furthermore, the keypress excitation can be clearly dissociated from the synaptic processes generating the N4/P3 (occurring simultaneously with the specific stimulus excitation) by the longer latency for keypress excitation and contrasting task correlates. Whereas N4/P3 amplitudes are strongly related to stimulus repetition, and affected little or not at all by whether the repeated or nonrepeated words are targets (Smith *et al.*, 1986), keypress excitation is not influenced by stimulus repetition but *is* strongly controlled by target designations (i.e., it is provoked by nonrepeated words if and only if they are keypress targets). Clearly, these very distinct behavioural correlates and longer latencies establish keypress excitation as a distinct stage in MTL information processing.

When two contrasting responses were required after two delays in four randomly intermixed conditions (the DCRM WORDs task), the keypress excitation was no longer found. Thus the keypress excitation response is not strictly associated with the decision or formulation of the actual keypress but appears to be dependent on the task governing the response. The dependence of MTL response-related activity on the rules governing response selection has been reported in monkey hippocampus by Brown (1982). The restriction of keypress excitation to target stimuli, its contextual dependence, and its relatively late onset latency are all consistent with its representing a 'matching' of the neuronally encoded stimulus (integrated with the contextual rules of the task) to a response template held in working memory (*see* Tulving, 1983). The matching presumably involves an interaction with frontal lobe structures, perhaps via medial frontal limbic areas. In this respect, it is interesting that cingulate gyrus units recorded in the RM WORD paradigm are activated during the same time period as the MTL keypress excitation. However, the cingulate gyrus units are excited both to target and nontarget stimuli, as might be expected if they were the source of the response criterion template to be matched by the MTL/posterior neocortex to the stimulus/context pattern. The MTL contribution to stimulus-response matching is thus considered to be analogous to its contribution to contextual encoding. In both cases, the MTL would contain a recent episodic trace uniting disparate neocortical elements. In stimulus-response matching, keypress excitation would help retrieve the appropriate response to the perceived category of the current stimulus, whereas in contextual encoding, specific excitation would help retrieve the integrated representation of a particular stimulus in the current context.

The early onset latency of the 'PERIKP' units (a mean of 256 ms *before* the keypress) is consistent with this interpretation, but 'POSTKP' units did not *begin* firing until about 40 ms *after* the keypress. This may be explained by supposing that the keypress, a very simple response, is released when a criterion has been reached due to the inputs of 'PERKIP' units, but that contextually based information may continue to accumulate following the keypress (represented by the POSTKP excitation). As noted above, behavioural performance in recognition memory also depends on an additional non-MTL source of information termed perceptual fluency. Presumably perceptual fluency information permits a more automatic and rapid stimulus-response coupling (resulting in keypress execution before completion of the stimulus-response mapping) than does retrieval of an integrated stimulus-context-response set. Consistent with this interpretation, shorter reaction times are observed in later blocks of recognition memory when the contribution of perceptual fluency is largest (Smith and Halgren, 1989).

Contextually dependent hippocampal stimulus-response coupling, operating in parallel with a more rapid and automatic process, may also explain the increased hippocampal unit firing reported in the rabbit by Berger and Thompson (1978) during the classically conditioned nictitating membrane response. Berger and Thompson observed that the hippocampal firing closely parallels the details of the conditioned movement itself, and suggested that it may help define those details. Yet the structures essential for acquisition of the conditioned response in rabbits lie in the deep cerebellar nuclei (Thompson, 1986). Classical conditioned responses in humans also appear to be independent of the MTL. Weiskrantz and Warrington (1979) described 2 temporal lobe amnesic patients who successfully acquired a pavlovian eye-blink conditioned response despite having no memory of the task. Therefore, both in animals and man, MTL unit response closely paralleling behaviour may occur in tasks in which behaviour is little affected by MTL lesions.

In summary, the behavioural correlates of MTL unit activity can loosely be categorized using a series of temporally ordered processes occurring after initial sensory analysis in each trial in all tasks. For every trial, the subject must encode the stimulus by integrating its previously learned meaning with the current cognitive context. Once these processes are actively terminated (closure), the results of this encoding and contextual integration are used to formulate and execute an appropriate response. Each of the functional stages of the encoding-closure-response cycle fits the timing and task correlates of one of the three distinct neural responses described here. The encoding phase is represented by the specific stimulus excitation to repeated stimuli, nonspecific excitation, and the early excitation to the infrequent stimuli in the auditory oddball discrimination task. The physiological correlate of closure, in turn, is the inhibition to infrequent tones in the auditory oddball discrimination paradigm, while response formulation and execution is related in some unknown way to keypress excitation.

This cycle of encoding, closure and response can be regarded as occurring simultaneously and in parallel in many regions of the nervous system. During this cycle, each functionally specialized region of the nervous system can contribute information with varying levels of criticality to the behavioural demands of the task. For example, the MTL is known from clinical studies to contribute information critical to the recognition process during recent memory. In a 'noncritical behaviour', the MTL could still be activated, but its contribution is no longer essential to the successful completion of that behaviour. Thus MTL behavioural firing correlates were consistent across tasks, regardless of whether or not a given task explicitly required recent episodic memory for normal performance. It should be noted that overall changes in firing-rate across tasks were not examined in this study, because the various tasks were not repeated several times in random order in each patient; therefore firing-rate differences between task could have been due to nonspecific drift resulting from physiological or technical influences.

We have proposed a series of temporally ordered events that use the functional specialization of the brain to evaluate and respond to stimuli. This cycle is thought to occur in multiple parallel processors, located throughout the nervous system. The output of the MTL processor is critical for the contribution of contextual retrieval from recent memory to the integration of stimulus meaning with the current context. Additional MTL activity may contribute to the release of the contextually appropriate response through interactions with response templates in other sites.

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MOOD DISORDERS AFTER STROKE AND THEIR RELATION TO LESION LOCATION

A CT SCAN STUDY

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SUMMARY

In a community-based study of stroke survivors, we identified 73 consecutive patients with a stroke, the first ever in a lifetime, who had a CT scan which showed a neurologically appropriate single stroke lesion, and who did not have a psychiatric disorder in the year preceding the stroke. A detailed follow-up study of these patients using standardized psychiatric assessments failed to confirm a number of recent claims about poststroke depressive disorders. We found no evidence that left-sided lesions were associated with more severe or persistent depressive symptoms, or that right-sided lesions were associated with hypomania. The DSM III syndrome of major depression was much less common than has previously been reported, and was not specifically associated with lesions placed anteriorly in the left hemisphere. There was a weak correlation between mood symptom scores and the proximity of the stroke lesion to the frontal pole of the hemisphere, but no evidence of a difference between right and left hemisphere strokes in the nature of the relationship between lesion distribution and mood symptoms. We suggest that previous studies have different findings because of differences in the conventions applied to the definition and measurement of psychiatric disorders after stroke, and because other studies have concentrated on selected inpatient populations.

INTRODUCTION

Workers at the Johns Hopkins University School of Medicine (JHMS) have published a number of papers in recent years on the nature of mood disorders after stroke, in which they have claimed that depressive disorders, in particular, have specific characteristics in stroke patients. They have argued that in this setting the DSM III syndrome of major depression is a discrete disorder which develops early (Robinson *et al.*, 1983), persists for much of the first 2 yrs poststroke, and is only weakly associated with the degree of physical disability caused by the stroke—especially in the early stages of recovery (Robinson *et al.*, 1984*a*). They contrast this early major depression with depressive states which, when they are seen later poststroke, are more strongly associated with physical disability (Robinson *et al.*, 1987). A central component of their hypothesis

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has been that major depression (but no other type) is associated with lesions in the anterior part of the left hemisphere, a phenomenon which is taken to indicate that the psychiatric syndrome is a direct manifestation of the focal neurological damage (Robinson *et al.*, 1984*a*, 1987). Related to this hypothesis has been the suggestion that right frontal lesions may be associated with undue cheerfulness, described by the Baltimore group as hypomania.

There are several reasons why these claims about mood disorder and lesion location are difficult to evaluate. First, the original topographical definition of anterior lesions (Robinson *et al.*, 1984*b*) was modified in a subsequent publication (Starkstein *et al.*, 1987). Neither definition identifies lesions in a particular anatomical site, so that although the original hypothesis suggested that cortical damage was the determining factor in the onset of major depression—and an animal model of such damage was described—later findings have also implicated subcortical lesions (Starkstein *et al.*, 1987). Secondly, the relationship between lesion location and mood disorder has been expressed in two apparently incompatible forms. The original report (Robinson *et al.*, 1984*b*) described a graded effect of lesion location on severity of mood change, which suggested that mood symptoms were continuously distributed and that there was a linear relationship between their severity and the proximity of the lesion to the frontal pole of the left hemisphere. In subsequent papers, however, major depression has been claimed to be a specific syndrome which can be delineated from so-called dysthymic depression, with the two types of depression associated with lesions in different parts of the brain (e.g., Robinson *et al.*, 1987).

The claims of Robinson and coworkers about the relationship between lesion location and mood disorder after stroke have become well known among neurologists and psychiatrists interested in this field. However, apart from the uncertainties referred to above, there are also difficulties in interpreting the research data upon which the group have based their conclusions. The main problems are that small numbers of selected stroke patients have been studied, and that methods of psychiatric assessment and of case definition have been modified from the original standardized versions. Only one attempt by another group to reproduce these findings has been published (Sinyor *et al.*, 1986), with equivocal results due mainly to the small numbers of patients included. We have therefore undertaken a study in which we have attempted as far as possible to test the hypotheses outlined above about the relationship between lesion location and mood disorder. We have avoided sampling bias by studying a consecutive series of patients seen in the Oxfordshire Community Stroke Project, and we have used standard psychiatric assessments. This study formed part of a wider investigation of psychiatric and social aspects of stroke, the results of which are being reported elsewhere.

PATIENTS AND METHODS

The Oxfordshire Community Stroke Project (OCSP)

The basis of the OCSP is a register of all new cases of transient ischaemic attack and first ever in a lifetime stroke occurring in a defined population of approximately 105 000 people. Particular efforts were made to obtain complete case ascertainment and follow-up of all cases. The full methodology of the OCSP has been reported elsewhere (Bamford *et al.*, 1988). Patients notified to the project were seen by a study neurologist either in hospital wards, in their own homes, or as outpatients. Less than half the stroke patients were admitted to hospital at the time of the acute episode. Overall disability was measured using the Barthel Index of Activities of Daily Living (Mahoney and Barthel, 1965); disability was assessed retrospectively for the patient's function immediately before the stroke as well as for the time of the neurological examination. CT brain scanning was undertaken in more than 90% of cases. The final diagnosis of stroke was made at a weekly clinical consensus meeting, using a modification of the WHO criteria (Aho *et al.*, 1980).

Patients

Patients interviewed for this study were first seen between March 1, 1986 and November 30, 1986, during which time 116 consecutive patients were seen by one of the study neurologists (M.D., C.W.) and diagnosed as having suffered a first ever in a lifetime stroke. Of these, 98 survived to 1 month and 95 (97%) were interviewed for the first time then; 89 of the 91 survivors (96%) were seen at 6 months, and 84/86 (98%) survivors were seen at 12 months after the stroke. A further 41 patients had been notified to the project between November 1985 and March 1986. Of these patients, 33 survived to 6 months and were seen for the first time them; 31/33 survived to 12 month interview. The patients seen for the study are summarized in Table 1.

TABLE 1. STROKE PATIENTS NOTIFIED TO THE OCSP BETWEEN NOVEMBER 1985 AND NOVEMBER 1986, WHO WERE FIRST INTERVIEWED FOR THIS STUDY BETWEEN APRIL 1986 AND DECEMBER 1986

	Notified Nov. 1985–Mar. 1986 (n = 41)	*Notified Apr. 1986–Nov. 1986 (n = 116)*	*Total*
1 month			
Alive	–	98	98
Seen	–	95	95 (97%)
6 months			
Alive	33	91	124
Seen	33	89	122 (98%)
12 months			
Alive	31	86	117
Seen	31	84	115 (98%)

Psychiatric assessments

Patients were usually interviewed in their place of residence; the only subjects seen in hospital were those who were inpatients at the time of follow-up. Psychiatric interviews were undertaken without knowledge of the CT scan findings or the results of the research neurologists' assessments. All the patients were interviewed (by A.H.) using the shorter version of the Present State Examination (PSE) (Wing *et al.*, 1974, 1977), a standardized psychiatric assessment designed for use in community surveys which is suitable for use with the elderly (Murphy, 1982) and the physically ill (Feldman *et al.*, 1987). The PSE takes the form of a semistructured interview which is administered and rated by a trained interviewer. With the addition of a few supplementary questions to the interview, the PSE provides enough information to allow a diagnosis to be given to identified cases of psychiatric disorder using the criteria of DSM III (American Psychiatric Association, 1980). Patients also completed the Beck Depression Inventory (BDI), a 21 item self report questionnaire which covers somatic, cognitive and affective symptoms of depression (Beck *et al.*, 1961). Those who were unable to complete the BDI because of language, praxic or other cognitive deficits did not have it administered to them. Dysphasia was assessed using the Frenchay Aphasia Screening Test (FAST)

(Enderby *et al.*, 1987). The mini-mental state examination (Folstein *et al.*, 1975) was used as a screening test for global cognitive impairment.

Radiological assessments

CT brain scans were performed using a Siemens Somaton DR1 scanner with 8 mm cuts and without contrast injection. A consultant neuroradiologist (A.M.) reported the anatomical site of any visible stroke lesion, and its pathological type. Reporting was undertaken without knowledge of the neurological or psychiatric status of the patients.

Lesions identified by the neuroradiologist were also localized according to two other methods. (1) The topographical criteria suggested by Robinson *et al.* (1984*b*) were applied. According to this method a lesion is anterior if no part extends > 60% caudally on any scan cut and some part extends < 40% rostrally, posterior if some part extends > 60% caudally and no part extends < 40% rostrally on any cut, and intermediate if it lies between both lines on all cuts (*see* fig. 1). Large lesions which cross both lines are classified as intermediate. (2) The shortest distance on any cut between the anterior border of the lesion and the anterior pole of the ipsilateral hemisphere was measured, and expressed as a percentage of the total anteroposterior length of that hemisphere at the same level. This variable is referred to as ANTPER in the text.

Lesion volume was estimated according to the method of Pullicino *et al.* (1980). Lesions were categorized following the same author as small (less than 4 ml), medium (4–10 ml), or large (greater than 10 ml); normal scans were placed in the small lesion group.

Data analysis

PSE data were analysed using the Catego/ID computer program (Wing *et al.*, 1978), which calculates a total symptom score and derives syndromes from combinations of the symptoms rated. The program also gives a measure of the severity of any psychopathology present—the Index of Definition (ID) (Wing *et al.*, 1978). Patients who score at ID levels 1–4 are considered noncases, and those at level 5 or above are cases of psychiatric disorder. Cases can then be given a diagnosis according to a standard classification system such as ICD 9 (World Health Organization, 1977) or DSM III.

Other data were analysed using the statistics package SPSS-X (Nie, 1983). Nonparametric tests of significance were used, with two-tailed tests of probability.

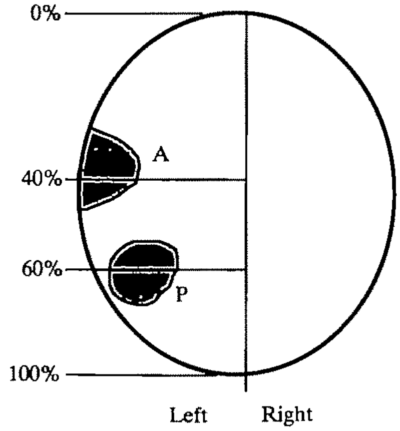

FIG. 1. Schematic representation of topographical criteria used by Robinson *et al.* at Johns Hopkins Medical School, to designate lesions visible on CT scan as anterior (A) or posterior (P). *See* text for details.

RESULTS

The patients

General characteristics of the patients

In the total cohort of 128 stroke patients who were seen at least once after their stroke, there were 58 men and 70 women. The mean age of the group was 71.2 yrs (range 18–96 yrs, SD 13.7). At the time of the stroke 26 (20%) were living alone, 84 (66%) were living with family, and 18 (14%) were in residential care. The proportion scoring less than full points on the Barthel ADL Index was 18/128 (14%) prestroke. This disability was mainly the result of arthritis or cardiac disease, but was associated with nonstroke neurological disorders in 2 cases, 1 with Parkinson's disease and 1 with multisystem degeneration.

Because the OCSP is a community-based study, many of the strokes were mild. Thus only 48/128 (38%) of the patients were admitted to hospital at the time of their stroke. The proportion scoring less than full points on the Barthel ADL was 58/128 (45%) at neurological assessment immediately poststroke. At 6 months only 3 patients were still completely wheelchair-bound and unable to walk even with assistance. At 12 months 14/115 (12%) of survivors were living in some form of professionally supervised residence because of stroke-related disability. There were no differences between patients with strokes in the left or right cerebral hemisphere on these measures of stroke severity. Thus 25/39 (64%) patients with a CT scan which showed a left hemisphere lesion had a Barthel score < 20, compared with 21/31 (68%) with a right hemisphere lesion on CT scan. Twenty out of 39 patients (51%) with left hemisphere lesions on CT scan and 18/31 (58%) with right hemisphere lesions were admitted to hospital at the time of their stroke.

For those interviewed at 1 month, dysphasia (defined as a score < 20 on the speech sections of FAST) was present in 19/95 (20%). Cognitive impairment (mini-mental test score ≤ 23) was found in 25/95 (26%) at 1 month, 26/122 at 6 months and 24/115 (21%) at 12 months.

On the basis of clinical presentation and CAT scan results, stroke subtype was determined as follows: probable or definite cerebral infarction 104 (81%); primary intracerebral haemorrhage 9 (7%); subarachnoid haemorrhage 4 (3%); no scan, subtype uncertain 11 (9%).

Psychiatric status of the patients

The Beck Depression Inventory (BDI) was completed by 76/95 (80%) patients at 1 month, 107/122 (88%) at 6 months and 88/115 (77%) at 12 months. Specific language difficulties without other cognitive impairment (i.e., dysgraphia/dyslexia) were the reason for failure to complete in 10 cases at 1 month, 5 cases at 6 months and 3 cases at 12 months. More patients were able to provide ratable answers for the Present State Examination (PSE): 89/95 (94%) at 1 month, 119/122 (96%) at 6 months and 112/115 (97%) at 12 months. It was possible to obtain sufficient information to give a DSM

III diagnosis to all patients who were able to complete the PSE interview.

We have reported in detail elsewhere our findings on the psychiatric symptoms found in this group of patients, and compared them with a general population control sample drawn from the same practices' age-sex registers (House *et al.*, 1990). Only the main results for the stroke patients will be presented here.

Scores on the BDI were continuously distributed, with a marked skew towards scores in the upper range. Over the year of follow-up there was a gradual reduction in symptom scores, so that the proportion scoring above a commonly used threshold for case identification ($\geq$ 13) fell from 20% at 1 month to 8% at 12 months. The reduction in scores on somatic items of the BDI was more marked than was the reduction in scores on the cognitive and affective items.

Total symptom scores derived from the PSE interview showed a very similar pattern. PSE syndrome for the stroke patients revealed a wide range of psychiatric symptoms, with so-called 'nonspecific' symptoms such as self-neglect, social withdrawal, worry and tension accounting for much of the total score. By comparison special features of depression such as guilt and suicidal ideas were uncommon.

Levels of diagnosable psychiatric disorder, defined according to Index of Definition from the PSE data, illustrated these same two points. There was a gradual reduction in psychiatric disorder over the year and there were a range of diagnosed psychiatric disorders which were not depressive. In fact the prevalence of DSM III major depression fell from 11% at 1 month to 5% at 12 months. Anxiety disorders persisted at a level of 6–7% throughout the year, and a range of behavioural and emotional problems which did not fit well into orthodox classifications were also encountered. One particularly common problem was an increased emotionalism—that is episodes of crying which were sudden or unheralded and not all under normal social control. Some 21% of patients complained of emotionalism at some time in the year after stroke. Although these patients tended to have more mood symptoms than those without emotionalism, the presence of emotionalism was often unaccompanied by diagnosable mood disorder (for details, *see* House *et al.*, 1989*a*).

We encountered no cases with euphoria, and nobody with the PSE syndrome of hypomania. One woman had persistent denial of handicap accompanied by minor depressive symptoms (House and Hodges, 1988). Of the two cases of pathological laughter (House *et al.*, 1989*a*), one had 3 discrete episodes and no persistent mood symptoms between them, and the other had a single episode and was mainly troubled by severe pathological weeping.

Very few patients had psychiatric disorder which persisted throughout the year. Of those who completed the BDI three times in the year ($n = 60$), only 2 had scores $\geq$ 13 on all three occasions. Only 3/78 (4%) patients who completed the PSE on all three occasions scored at a level of severity high enough to be labelled a case (ID $\geq$ 5) every time, and major depression persisted throughout the year in 2/78 (3%) who were interviewed at 1, 6 and 12 months.

Eight patients had psychiatric disorder in the 12 months *before* their stroke. These patients either described a clear onset of mood disorder which met DSM III criteria for a psychiatric diagnosis, and which antedated the stroke and persisted to the time of the first interview, or they were receiving psychiatric treatment at the time of the stroke. At 1 month 5/17 (29%) cases identified on Catego/ID were in this 'chronic' group, and all had a diagnosis of major depression at interview.

Findings on CT brain scan

A CT brain scan was obtained in 117/128 (91%) of the stroke patients. The scan showed no stroke lesion in 42 cases and a lesion appropriate to the neurological presentation in 75/128 (59%) cases. Using broad anatomical categories the stroke lesions in the 75 'positive' scans were localized as follows: brainstem/cerebellar n = 5; other subcortical structures (thalamus, basal ganglia) with no cortical involvement n = 29; cortical structures involved (± subcortical lesion) n = 41. In the 41 cases with cortical lesions, 9 (22%) were restricted to one lobe only, and 32 (88%) involved more than one lobe. The frontal lobe was involved (alone or with other structures) in 16/41 (39%) cases.

Lesion location according to the Johns Hopkins topographical criterion is given in Table 2, which shows that 14/128 (11%) had a left anterior lesion of the sort claimed to be significant in the aetiology of major depression.

There was no difference in the size of stroke lesions identified in positive CT scans when patients with left or right cerebral hemisphere lesion were compared (mean volume: right = 37.6 ml (SD 34.9); left = 41.2 ml (SD 40.8)).

TABLE 2. CLASSIFICATION OF LESION LOCATION ON CT SCANNING, ACCORDING TO THE TOPOGRAPHICAL CRITERION OF ROBINSON *et al.* (1984*b*)

	Anterior	*Posterior*	*Intermediate*	*Uncertain*	
Right	9	9	13	0	= 31
Left	14	11	10	4	= 39
				Brainstem/cerebellar	= 5
				No stroke lesion	= 42
				No scan	= 11
				Total	128

The relationship between mood disorder and CT scan findings

Two patients with a positive CT scan had a history of psychiatric disorder with onset in the year preceding the stroke; that is, although they had diagnosable mood disorder at research interview, they gave a clear history that this had developed before the stroke and persisted into the poststroke period. Patients with a history of treatment for psychiatric disorders in earlier life (but not the year before stroke) were not excluded. Neither patient with a pre-existing neurological disorder had a stroke lesion visible on CT scan. There were 73 patients with a positive CT scan and no psychiatric disorder in the year before their stroke. Data on lesion laterality and localization are given for patients with scans showing cortical or subcortical lesions in the cerebral hemispheres, and the scans showing posterior fossa lesions are excluded.

Total symptom scores for the PSE and BDI at each interview were compared for patients with lesions visible in the left and right cerebral hemispheres (*see* Table 3). At none of the 3 interviews was there a significant difference in PSE or BDI scores between the two groups. The relationship of side of lesion to diagnosable psychiatric disorder—defined as ID ≥ 5—was also examined (Table 4). Using a χ^2 analysis to examine the distribution of ID in those with right and left lesions, there was again no evidence that psychopathology was more frequent at any interview in those with left-sided lesions.

When lesions were categorized according to the Johns Hopkins criteria as anterior, intermediate or posterior, there was no evidence of an effect of lesion location on PSE or BDI scores at 1, 6 or 12 months using a Kruskal-Wallis one-way ANOVA.

TABLE 3. MEAN TOTAL SCORES (SD) ON THE PRESENT STATE EXAMINATION (PSE) AND BECK DEPRESSION INVENTORY (BDI), FOR PATIENTS WITH A STROKE LESION VISIBLE IN THE RIGHT OR LEFT CEREBRAL HEMISPHERE ON CT SCAN

	Right hemisphere lesion	*Left hemisphere lesion*	*Significance (Kruskal-Wallis ANOVA)*
1 month			
PSE score	6.8 (6.2)	7.5 (5.7)	χ^2 1.93
Mean (SD)	(n = 21)	(n = 19)	n.s.
BDI score	7.5 (6.3)	7.5 (4.7)	χ^2 1.69
Mean (SD)	(n = 19)	(n = 17)	n.s.
6 months			
PSE score	5.8 (5.5)	5.3 (4.2)	χ^2 0.03
Mean (SD)	(n = 30)	(n = 33)	n.s.
BDI score	7.2 (6.0)	8.5 (5.7)	χ^2 2.59
Mean (SD)	(n = 28)	(n = 28)	n.s.
12 months			
PSE score	5.4 (4.9)	4.3 (3.3)	χ^2 2.78
Mean (SD)	(n = 27)	(n = 31)	n.s.
BDI score	5.8 (5.0)	5.5 (4.4)	χ^2 0.29
Mean (SD)	(n = 21)	(n = 20)	n.s.

TABLE 4. PROPORTION OF PATIENTS WITH A VISIBLE CT SCAN LESION IN THE CEREBRAL HEMISPHERES WHO WERE ABLE TO COMPLETE THE PSE INTERVIEW AND HAD A PSYCHIATRIC DISORDER (AS DEFINED BY THE CATEGO-ID): RELATIONSHIP OF PSYCHIATRIC DISORDER TO THE SIDE OF THE BRAIN LESION

	1 month		*6 months*		*12 months*	
	ID 1–4	*ID ≥5*	*ID 1–4*	*ID ≥5*	*ID 1–4*	*ID ≥5*
R cerebral hemisphere lesion	16/21 (76%)	5/21 (24%)	23/30 (77%)	7/30 (23%)	23/27 (85%)	4/27 (15%)
L cerebral hemisphere lesion	16/19 (84%)	3/19 (16%)	29/33 (88%)	4/33 (12%)	30/31 (97%)	1/31 (3%)
Difference in proportion of ID ≥5 (R vs L) (95% CI)	8% (−5 to 45%)		11% (−8 to 30%)		12% (−11 to 35%)	

ID = Index of Definition.

The relationship between diagnosable disorder—according to DSM III criteria—and lesion location is shown in Tables 5 and 6. There was no overall significant association between major depression and lesion side or location on the JHMS criteria. In fact only 1 patient has the combination of major depression and a left anterior lesion at 1 month interview, 3 patients had that combination at 6 months, and none had it at the 12 month interview.

There was an association between total symptom scores on the BDI and PSE, and the distance of the anterior border of the stroke lesion from the anterior pole of the hemisphere in which it lay. Although the size of the effect was not great, there was a negative correlation between the two measures, indicating that the more anteriorly the lesion extended then the more mood symptoms were present (*see* top row, Table 7).

TABLE 5. RELATIONSHIP BETWEEN PSYCHIATRIC DISORDER (AXIS 1; DSM III) AND SIDE OF LESION ON CT SCAN (PATIENTS WITH LESIONS IN CEREBRAL HEMISPHERES ONLY)

	R hemisphere lesion	*L hemisphere lesion*	*Normal scan*
1 month			
Major depression	3 (14%)	1 (5%)	4 (11%)
Other diagnosis	8 (38%)	6 (32%)	8 (22%)
No diagnosis	10 (48%)	12 (63%)	25 (67%)
Total	21	19	37
6 months			
Major depression	4 (13%)	3 (9%)	4 (9%)
Other diagnosis	11 (37%)	3 (9%)	9 (19%)
No diagnosis	15 (50%)	27 (82%)	33 (72%)
Total	30	33	36
12 months			
Major depression	2 (7%)	1 (3%)	3 (7%)
Other diagnosis	7 (23%)	3 (10%)	8 (20%)
No diagnosis	18 (70%)	28 (87%)	20 (73%)
Total	27	31	41

TABLE 6. RELATIONSHIP BETWEEN LESION LOCATION (JHMS CRITERIA) AND THE PRESENCE OF MAJOR DEPRESSION AT EACH FOLLOW-UP INTERVIEW, FOR STROKE PATIENTS WITH LESIONS VISIBLE IN THE LEFT OR RIGHT CEREBRAL HEMISPHERE ON CT SCANNING

	1 month Major depression		*6 months Major depression*		*12 months Major depression*	
	Present	*Absent*	*Present*	*Absent*	*Present*	*Absent*
Anterior						
Right	0	7	2	7	0	9
Left	1	7	3	9	0	11
Posterior						
Right	3	5	2	11	0	8
Left	0	5	0	10	0	10
Intermediate						
Right	0	6	0	8	2	11
Left	0	6	0	11	0	10

TABLE 7. RELATIONSHIP* BETWEEN TOTAL SYMPTOM SCORES ON THE BDI AND PSE, AND DISTANCE OF ANTERIOR BORDER OF STROKE LESION FROM ANTERIOR POLE OF THE HEMISPHERE (ANTPER), FOR PATIENTS WITH A CT SCAN SHOWING A LESION CONFINED TO THE RIGHT OR LEFT CEREBRAL HEMISPHERE

	1 month		6 months		12 months	
	BDI	PSE	BDI	PSE	BDI	PSE
All lesions	−0.057 (n = 35) n.s.	−0.25 (n = 40) $P = 0.05$	−0.29 (n = 56) $P = 0.01$	−0.28 (n = 63) $P = 0.01$	−0.089 (n = 41) n.s.	−0.18 (n = 58) $P = 0.08$
R hemisphere lesions	−0.05 (n = 19) n.s.	−0.23 (n = 21) n.s.	−0.34 (n = 28) n.s.	−0.23 (n = 30) n.s.	−0.19 (n = 21) n.s.	−0.09 (n = 27) n.s.
L hemisphere lesions	−0.002 (n = 17) n.s.	−0.1 (n = 19) n.s.	−0.21 (n = 28) n.s.	−0.38 (n = 33) $P = 0.05$	+0.39 (n = 20) n.s.	−0.02 (n = 31) n.s.

* Spearman's rank order correlation coefficients. All values for $P < 0.1$ given in table.

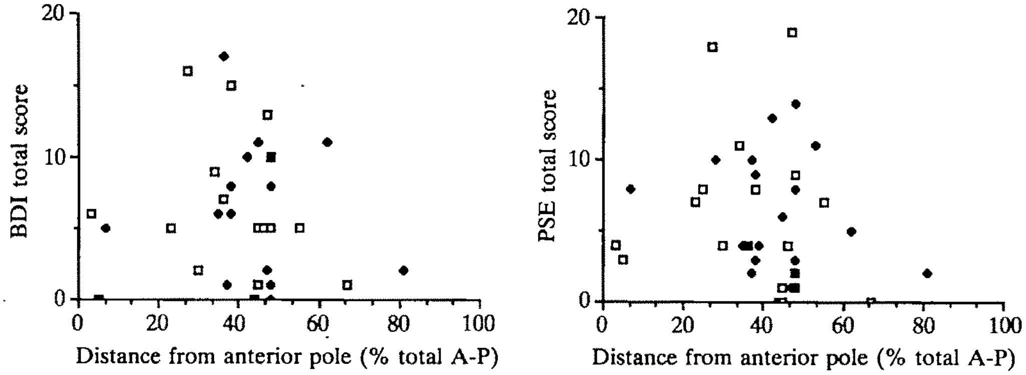

FIG. 2. Scatterplot showing relationship between BDI and PSE scores at 1 month, and proximity of the anterior border of the stroke lesion to the frontal pole of the hemisphere (ANTPER). Open squares = right-sided lesion; closed diamonds = left-sided lesion.

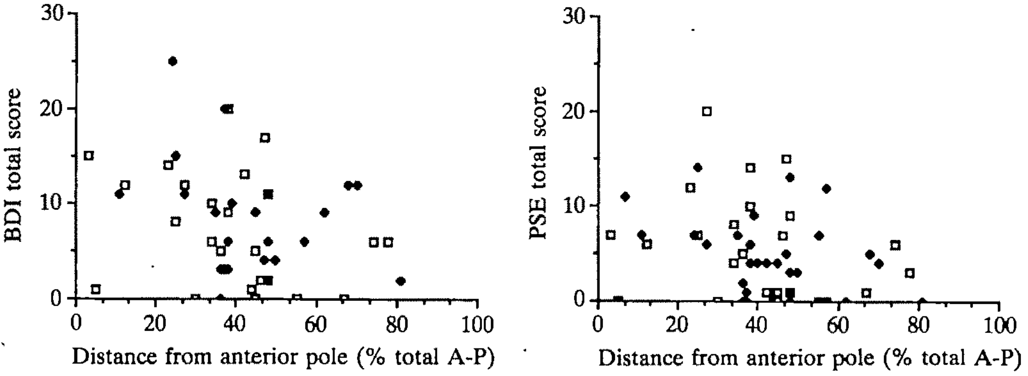

FIG. 3. Scatterplot showing relationship between BDI and PSE scores at 6 months, and proximity of the anterior border of the stroke lesion to the frontal pole of the hemisphere (ANTPER). Symbols as in fig. 2.

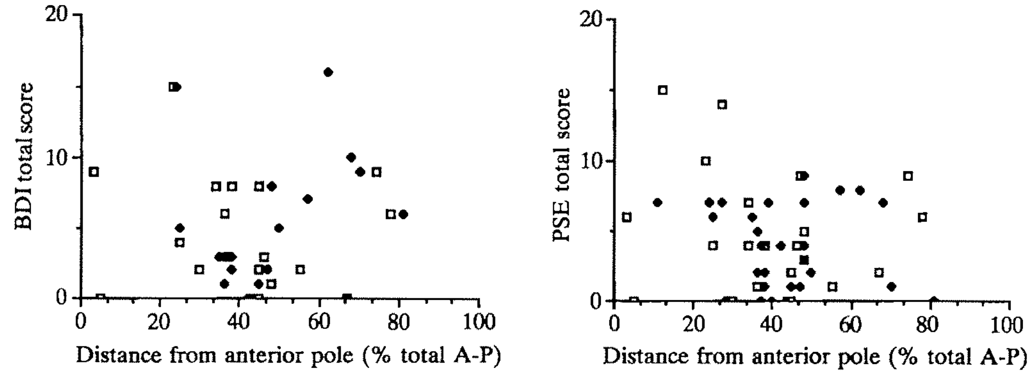

FIG. 4. Scatterplot showing relationship between BDI and PSE scores at 12 months, and proximity of the anterior border of the stroke lesion to the frontal pole of the hemisphere (ANTPER). Symbols as in fig. 2.

This finding was apparently true for both right and left sided lesions (*see* figs 2–4). The reduction in numbers entailed in examining the two sides independently meant that most of the correlations were no longer statistically significant, but the trends were all in the same direction for right and left-sided lesions considered separately as they were for the whole group (Table 7).

A possible explanation for this finding is that lesion volume accounts for the effect, that is, larger lesions might be more likely to extend anteriorly simply by virtue of their size, and might be in themselves associated with more depressive symptoms. In fact there was a suggestion of a weak correlation between lesion volumes and ANTPER (Spearman's correlation $r_s = -1.9$, $n = 73$, $P = 0.052$), and between volume and the measures of mood made at 1, 6 and 2 months (*see* Table 8). However, when lesions on the CT scan were subdivided according to size, the correlation between ANTPER and mood actually appeared stronger in the patients with smaller lesions (*see* Table 9). An attempt was made to examine this relationship further by transforming the data so they could be entered into a multiple regression analysis with mood as the dependent variable, and volume and ANTPER as independent variables. Unfortunately, the correlations were insufficiently strong to allow this; after transformation neither independent variable met the criteria for entry in a forward regression against any of the mood measures used as a dependent variable (further details available from authors).

TABLE 8. RELATIONSHIP* BETWEEN TOTAL SYMPTOM SCORES ON THE BDI AND PSE, AND VOLUME OF THE STROKE LESION, FOR PATIENTS WITH A CT SCAN SHOWING A CLINICALLY APPROPRIATE STROKE LESION

1 month		*6 months*		*12 months*	
BDI	*PSE*	*BDI*	*PSE*	*BDI*	*PSE*
−0.15 (n = 39) $P = 0.19$	+0.01 (n = 46) $P = 0.46$	+0.19 (n = 59) $P = 0.08$	+0.18 (n = 67) $P = 0.07$	+0.11 (n = 47) $P = 0.22$	+0.21 (n = 62) $P = 0.05$

* Spearman's rank order correlation coefficients.

TABLE 9. RELATIONSHIP* BETWEEN ANTPER AND SYMPTOM SCORES AT DIFFERENT INTERVIEWS, ACCORDING TO THE VOLUME OF THE STROKE LESION VISIBLE ON CT SCAN (CEREBRAL HEMISPHERE LESIONS ONLY)

	1 month		*6 months*		*12 months*	
	BDI	*PSE*	*BDI*	*PSE*	*BDI*	*PSE*
Lesions ≤ 10 ml	−0.22 (n = 25) n.s.	−0.35 (n = 27) $P = 0.04$	−0.28 (n = 34) $P = 0.03$	−0.33 (n = 34) $P = 0.05$	−0.08 (n = 28) n.s.	−0.07 (n = 33) n.s.
Lesions > 10 ml	+0.1 (n = 14) n.s.	+0.32 (n = 19) n.s.	−0.18 (n = 25) n.s.	−0.19 (n = 33) n.s.	−0.09 (n = 19) n.s.	−0.17 (n = 29) n.s.

* Spearman's rank order correlation coefficients.

DISCUSSION

In the Discussion we will consider methodological issues, and then review the results of our study in relation to the hypotheses which it was designed to test. Where we did not substantiate the main findings of Robinson and colleagues, we will suggest reasons for our different conclusions.

Total scores on the two measures that we employed were continuously rather than bimodally distributed, a finding which suggests that differences in depressive disorders in this population are a matter of degree rather than type. However, so that the hypotheses outlined above could be tested we have presented data on psychiatric state not only as total symptom scores but also in the nomenclature of DSM III. In presenting total symptom scores we have used the untransformed data from one self-report and one interview measure. We chose these measures because they have been used widely in research into the psychiatric sequelae of physical illness; we have reported elsewhere our findings on the validity of the BDI in stroke patients (House *et al.*, 1989*b*) and we chose the PSE principally with the aim of attempting to replicate the findings of the Johns Hopkins group.

There are limitations on the value of CT scanning as the means of lesion location in studies of stroke. Many patients who have undoubtedly had a stroke on clinical criteria have a CT scan which shows no clinically appropriate lesion (Sandercock *et al.*, 1985), and by the same token even those with visible lesions may have vascular damage in other parts of the brain which does not show on the scan. Although CT scanning can give accurate information on the localization and pathological type of stroke, dynamic studies show altered function in areas of brain extending well beyond the visible structural lesion (Baron *et al.*, 1986). The main advantage of CT scanning is that, despite these drawbacks, it is a feasible technique for assessment of large numbers of patients and it was for that reason that it was employed in this study.

In summary, we were testing three broad hypotheses about the relationship between mood and lesion location. First, that there is an effect of *side* of lesion on *type* of mood disorder, such that left hemisphere strokes are associated with depression and right hemisphere strokes with undue cheerfulness or hypomania. Secondly, that there is an effect of *site* of lesion within the hemisphere on *type* of mood disorder, such that left anterior lesions are associated with major depression. Thirdly, that there is an effect of *side* and *site* of lesion on *severity* of mood disorder, such that left anterior lesions are associated with more severe and more persistent depressive symptoms in the first year after stroke.

For the first hypothesis, we failed to find a relationship between the side of the brain affected by stroke and any subsequent mood disturbance, as judged by overall symptom levels or by the presence of diagnosable psychiatric disorder. Our findings are in keeping with recent stroke research which has localized lesions clinically rather than radiologically (Feibel and Springer, 1982; Ebrahim *et al.*, 1987; Wade *et al.*, 1987). We found no cases which warranted a PSE rating of hypomania. Similarly, we found no evidence to support the third hypothesis, since symptom scores in the patients with left brain lesions were no higher at either follow-up interview than were scores in patients with strokes affecting the right brain.

The findings in relation to the second hypothesis were not entirely negative. There was no evidence for an association between left anterior lesions (as defined by the JHMS topographical criterion) and major depression; for example, at 1 month poststroke this combination was found in only 1/89 patients. However, there was a correlation between symptom scores and proximity of the anterior border of the stroke lesion on CT scan to the frontal pole of the hemisphere. The correlation was much weaker that that found by Robinson *et al.* (1984*b*), but was in the same direction as that suggested by their findings in left hemisphere strokes. Sinyor *et al.*, 1986 found a nonsignificant trend in the same direction. We did not find the relationship between lesion distribution and mood symptoms to be different for patients with right hemisphere lesions from that found in those with left hemisphere lesions.

One explanation for the association between anteriorly placed lesions and mood symptoms might be that larger lesions are simply more extensive, and are associated with depression in their own right, perhaps because they are associated with greater physical disability or intellectual impairment. We were unable definitely to confirm or refute this suggestion with the numbers in our sample, because of the small size of the effect. Our results, although equivocal, in general argue against this interpretation as do those of Robinson *et al.* (1984*b*). The main alternative explanation is that the proximity of the stroke lesion to the frontal pole is in its own right—that is independently of its size—a factor in producing mood disturbance. Our results did provide some evidence to support this explanation. If this is the case then our data suggest that the effect is a weak one, and that there is no difference (in this respect) between left and right frontal damage in the influence it exerts on mood. Nonetheless this is an interesting possibility that merits further investigation.

What are the reasons for the difference between our results and those of the studies that prompted our study? A review of the literature suggests that the frequency and specificity of depression as a complication of stroke has been overemphasized as a result of variations in the use of diagnostic criteria, and by the study of selected patient groups (House, 1987). Problems with sampling bias could also have applied to studies on the importance of lesion location. For example, only 14 (11%) of our patients had a left anterior lesion as defined by JHMS criteria, so that even if a strong association with major depression and this lesion location had been found, it could not have accounted for the onset of major depression in more than a small minority of the total group of stroke patients. This argument indicates that in an unselected sample of stroke patients the *population* risk of major depression attributable to lesion location is low, but it does not exclude the possibility that there is an increased *relative* risk of depression in patients with left anterior lesions. Our results do not support such a suggestion, and we offer two explanations which might account for this contradiction of the Johns Hopkins findings.

The first explanation concerns the definition and identification of emotional disorders associated with brain damage. There is a considerable literature which indicates differences in the emotional behaviour of patients with right and left brain lesions. Studies of patients with right brain damage have noted a characteristic style in dealing with problem-solving situations, social interactions and perception of personal disability. Common themes are impaired self-monitoring and difficulties in the perception and expression of appropriate emotion, so that the patients appear apathetic, indifferent or perhaps fatuous, excessively jocular or euphoric (Bear, 1983; Heilman and Valenstein, 1985). By contrast, patients with left brain damage more readily respond to such situations with episodic distress, tearfulness or irritability (Goldstein, 1948; Gainotti, 1972). The former state is not the same as so-called symptomatic mania, lacking many of that condition's diagnostic features (Krauthammer and Klerman, 1978; Cummings and Mendez, 1984). The emotionalism associated with left brain damage has been distinguished from other depressive states by its episodic nature and specific relationship to testing situations (Gainotti, 1972). We would support these distinctions. In another part of our own study we found that emotionalism overlapped with but was not synonymous with psychiatrically diagnosable depression, and *was* associated (unlike major depression) with left anterior lesions (House *et al.*, 1989*a*). We encountered apathy/indifference and (rarely) denial of handicap after stroke, but no cases of hypomania. These problems are not mentioned in much of the recent research on the psychiatric sequelae of stroke, perhaps because they are not well described by orthodox psychiatric nomenclatures and because there are no accepted standardized measures of them. If instead of being treated separately, emotionalism has not been differentiated from depression in other studies, this would account for part of the differences from our findings. The differences in findings on hypomania probably arise from differences in rating conventions. The Johns Hopkins group use this PSE item to describe states which are not euphoric, excited or elated, while it is these characteristics which are rated in standard British usage of the PSE and which we rated in our own study.

A second possible explanation lies in the fact that the Johns Hopkins group have tested their hypothesis on lesion location in samples of hospital inpatients. Studying only admitted patients may result in the demonstration of a spurious association between the two variables (disease, risk factor) in a case control study, if the putative risk factor (in this case lesion location) is in itself associated with an increased risk of hospital admission—a problem sometimes called Berkson's bias (*see* e.g., Roberts *et al.*, 1978;

Sackett, 1979). This is not an implausible suggestion, since patients with left hemisphere strokes might be more commonly admitted because of the greater handicap associated with speech difficulty or dominant limb weakness. One British study found that once in hospital, patients with right hemiparesis were more likely than those with left hemiparesis to be admitted to a general medical rather than a geriatric ward (Brocklehurst *et al.*, 1978), suggesting that care needs to be taken in sampling even within a population of hospital inpatients. In the study of Robinson *et al.* (1984*b*), the ratio of left:right brain strokes was 22:14 (1.6:1). The influence of this bias on calculation of relative risk can be substantial, if difficult to estimate (Vessey, 1979).

The stroke patients that we studied were undoubtedly mild as compared with an inpatient series. Could this explain our failure to find an association between depression and left anterior lesions? The low rate of major depression in our patients raises the possibility of a Type II error, but there was no indication from our data of a trend in the hypothesized direction. If anything, there were more diagnosed mood disorders in patients with right hemisphere strokes. If lesion location—rather than lesion size, resultant disability, etc.—is one of the most important variables in determining the onset of depression after stroke, one might expect to see an association between depression and lesion location *more* readily in a population where other factors are less important.

In summary, our conclusion is that lesion location is not an important factor in determining the emergence after stroke of mood disorders which are diagnosable using orthodox psychiatric classifications. A study of long-term survivors from the Oxfordshire Stroke Project has reached the same conclusion (Sharpe *et al.*, 1990). One reason for contrary findings by other workers may have been an overemphasis on 'standard' psychiatric diagnosis at the expense of disorders such as pathological emotionalism which *are* associated with lesion location. Studies which only include selected inpatient samples have probably overestimated both the frequency of major depression in unselected stroke populations, and the contribution which lesion location could make to the onset of depression in such populations even if it were a cause of the depression. Berkson's admission-rate bias may produce a spurious association between left anterior lesions and depression. We have found some confirmation for the finding that there is a weak graded relationship between unpleasant mood symptoms and the proximity of the lesion to the anterior pole of the hemisphere but we have found no evidence for a difference between the two hemispheres in this respect.

If progress is to be made in elucidating the relationship between acquired brain damage and its emotional and behavioural consequences, then future studies in this field will need to address further these issues of selection in study populations, and definition and measurement of psychiatric variables.

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IMPAIRED MEMORY FOR NEW VISUAL FORMS

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SUMMARY

A case study is presented of a female patient who has had impairment of visual recent memory following damage to the right cerebral hemisphere from rupture of a middle cerebral artery aneurysm. Her ability to remember unfamiliar faces is severely impaired in comparison with controls, as is her ability to identify the faces of celebrities who have become famous since the time of her illness in 1985. By contrast, she performs well on tests of recognition memory for words and has no problem in identifying celebrities from their names. She is also good at identifying faces of people who became famous before her illness. On tests of episodic memory, she continues to perform well at remembering familiar faces and objects, regardless of whether the test demands memory for which face/object was presented or memory for which view of a face/object was presented. Her poor memory for visual material is confined to unfamiliar faces and objects. Consequently, it is evident that she can learn new visual information so long as it relates to a familiar visual form; it is the learning of new visual forms that is impaired. A final experiment revealed that she is also poor at remembering unfamiliar voices. This raises the possibility that the basic deficit affects recent nonverbal memory and is not confined to the visual modality. Overall, the findings have important implications for the nature of recent visual memory loss, and for the way in which visual information is stored in memory.

INTRODUCTION

Investigations of the impairments of visual recognition that can follow brain injury have shown that these can take a number of different dissociable forms (Hay and Young, 1982; Ratcliff and Newcombe, 1982; Warrington, 1982). The existence of these different types of impairment has crucial implications for models of visual recognition (Humphreys and Riddoch, 1987; Young, 1988), since it demonstrates that modular organization of function may be as characteristic of 'higher' as it is of more basic visual abilities (Cowey, 1985). Furthermore, by studying the different forms of impairment, much can be learnt about the nature and operation of the functional modules that subserve visual recognition.

To date, most studies have concentrated on the clinically salient visual agnosias. Nevertheless, the neurological literature also contains details of a small number of patients who, as a result of right hemisphere damage, appear to suffer from what Ross (1980, 1982) has termed 'isolated loss of visual recent memory'. It is known from the pioneering work of Milner and her colleagues (e.g., Milner, 1958, 1962, 1968) that left temporal

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lesions can selectively impair verbal memory, whereas right temporal lesions can impair memory for visual information. The pattern displayed by Ross' patients was particularly striking, however. They found it extremely difficult to learn new visual and spatial information, yet they remained able to recognize previously learnt material. They therefore had severe problems in recognizing the faces of people that they met in the period following their illness, but could still recognize old acquaintances. They had difficulties in orientating themselves in new environments, yet they were not lost in their old haunts. In experiments, they found it hard to reproduce unfamiliar objects as drawings a few minutes after presentation. Conversely, these patients did not appear to exhibit the same level of impairment on tests of verbal memory that they encountered with recent visual memory.

Patients of this type are potentially of considerable theoretical significance. Not only are they consistent with a dissociation between the encoding and the retrieval of visual information, they also suggest that one should distinguish verbal long-term memory functionally, and therefore perhaps anatomically, from the memory system that encodes new visual information.

Over the last 18 months, we have had the opportunity of studying in depth a patient who appears to have a similar pattern of deficit to previously reported cases. Our study has had two main aims. First, this patient has been investigated because neither of the 2 cases reported by Ross (1980) suffered *exclusively* from recent visual memory loss. The first patient that he described could not recognize premorbidly familiar faces any better than new faces, while his second patient could not remember previously well-known routes. Patients who have problems in recognizing new faces have also been described by Speedie and Heilman (1983) and Tranel and Damasio (1985). In neither case, however, was any information given concerning these patients' knowledge of people's names. Furthermore, Speedie and Heilman provided no details about their patient's ability to recognize premorbidly familiar faces. We therefore set out to provide more solid evidence for the existence of recent visual memory loss by employing more formal testing procedures than has sometimes been used in previous studies, and by using properly matched control subjects to provide appropriate baselines.

The second, and equally important, aim of our study was to investigate in more detail the precise *nature* of the problems encountered by a patient of this kind, in order to learn about the psychological processes involved in recognizing and remembering new visual stimuli. In so doing, we were able to demonstrate that although our patient was very poor at remembering the appearance of unfamiliar visual stimuli, she could learn instances of previously familiar visual forms without difficulty. These findings have important implications for the nature of visual memory loss, and for the way in which visual information is stored in memory.

CASE REPORT

Clinical history

E.L.D. is a right-handed woman who was born in 1936. She had a reasonably successful academic record at school obtaining 7 'O-levels' and 1 'A-level'. She lives in a city in north-east England where she was employed for many years in a job with a fair degree of responsibility, until she left in the mid-1970s to take over the running of a small post office.

In September 1985, E.L.D. had an acute neurological illness related to rupture of a right middle cerebral artery aneurysm which produced a haematoma in the sylvian fissure. A CT scan, performed in the following month, showed an extensive area of infarction in the right frontotemporal region with displacement of the hemisphere to the left. An angiogram in early October revealed a large middle cerebral artery aneurysm and also moderate vascular constriction. Shortly following this, the aneurysm was clipped via a right frontotemporal craniotomy. The operation was uncomplicated and there was no evidence of any further damage having occurred as a consequence. The patient made a rapid clinical recovery and was discharged at the end of November. She now lives on her own, having never married, although with a wide circle of supportive friends.

Spontaneous complaints

E.L.D.'s main spontaneous complaint concerns memory problems which, she claims, started to occur from the time of her acute illness. She claims to have become generally 'forgetful', often failing to remember appointments that she had made. The two major problems that she reports, however, are an inability to recognize the faces of people that she has met since the time of her illness, and problems in finding her way home. The problem with new faces is a source of social embarrassment for her and it also makes it difficult for her to follow television dramas in which unfamiliar characters appear. Nevertheless, she remains keen on reading fiction.

E.L.D. describes her topographical problems as resulting from an inability to form a mental picture of routes on which she has recently travelled. She states that she relies on the recognition of familiar landmarks to discover where she is. She lives in a new flat in an area with which she was unfamiliar before her illness, and for some time she found it difficult to alight at the appropriate bus stop following a trip to the city centre. She also states that she sometimes wakes up in the middle of the night quite unable to remember the layout of her room in the darkness. All this is consistent with a loss of *recent* visual memory. In addition, she claims to experience no difficulties in orientating herself in her parents' house or in her sister's house until she recently moved, both of with which she was familiar before her illness. She says that she can remember clearly the layout of the shop that she ran while working as a post mistress. She also showed a normal level of performance when we gave her a map of England and asked her to mark 15 major cities in their appropriate locations.

However, she also reports difficulties in finding her way around the city when out shopping. Since she lived there for many years before her illness, this would superficially appear to reflect retrograde as well as anterograde topographical amnesia. The situation, however, is complicated by the fact that the city centre has changed considerably in recent years and many of the changes coincided with the period in which she lived quite some distance away while working as a post mistress. Consequently, it appears that E.L.D.'s topographical problems are primarily associated with new rather than previously well-known environments. The present study, however, has concentrated on E.L.D.'s ability to process and remember faces and objects.

Perceptual processing

E.L.D.'s basic visual abilities are to some extent impaired. Contrast sensitivity is slightly impaired above 3 cycles/deg. Colour vision is also quite impaired (total error score of 274 on the Farnsworth-Munsell 100 hue test). There is, however, no evidence that these problems are directly connected with her visual memory difficulties since all our tests have suggested that she shows normal perceptual processing of words, objects and faces. Moreover, patients with impaired contrast sensitivity do not, of course, invariably have problems with recent visual memory.

Object recognition was initially tested by selecting 36 line drawings of living and nonliving items from Snodgrass and Vanderwart (1980), which were matched for frequency, concreteness and proportion of controls who had named the pictures correctly. Eighteen of these items were presented to E.L.D. as pictures which she was asked to name. The remainder were presented as words on index cards which she was asked to define. She named 18/18 correctly and provided excellent definitions for the remaining 18. Recognition and naming of photographs of everyday objects taken from prototypical and unusual views (*see* Warrington and Taylor, 1978) were also unimpaired (40/40). She also performed within the normal range (30/32 on 'easy' and 27/32 on 'hard' items) on a shortened version of an 'Object Decision Test' (*see* Riddoch and Humphreys, 1987, p. 143) which requires the subject to detect anomalous line drawings of objects and animals (e.g., a zebra's head on a tiger's body). Finally, a reaction time study has shown that she can recognize objects at normal speeds. Using a voice key, she took an average of 895 ms to classify each of 16 slides of real objects projected onto a screen as familiar, and an average of 1233 ms of reject 16 slides of unfamiliar objects. She made no errors on the 32 trials. Ten control subjects of comparable age gave mean reactions times (RT) of 904 ms (SD 153 ms) to familar objects and 1452 ms (SD 469 ms) to unfamiliar objects. Controls also made no errors.

E.L.D.'s ability to match faces also seems to be normal. She scored 44/54 on the Benton Facial Recognition Test (normal range 40–54). She scored 40/40 correct on a task which involved classifying the sex of an unfamiliar face (this task used both 'easy' and 'difficult' faces drawn from the study by Bruce *et al.*, 1987), and 40/40 on a task which involved classifying a face as young or old. She also performed well at judging facial expressions, successfully matching the expression as same or different on 30/32 pairs of faces of different unfamiliar faces (control mean = 29.79).

There is also no evidence of visual neglect. She performed well on a task which involved crossing out circles on the left and right-hand side of a piece of paper. She also read perfectly 40 four-letter words (from Ellis *et al.*, 1987*a*) with substitutable first letters.

General intellectual ability

E.L.D.'s Verbal IQ on the Wechsler Adult Intelligence Scale was 119 when tested in January 1987, which suggests that there has been no significant deterioration in general intellectual functioning. This conclusion is consistent with her performance on the National Adult Reading Test (NART) which estimated a premorbid Verbal IQ of 120. Performance IQ score was 100, and was lower than the score of 117 that would be predicted from the NART. Such a discrepancy between Verbal and Performance IQ is not unusual in a patient with this type of clinical background, and is consistent with the view that there may have been some reduction in intellectual capacity on tasks sometimes associated with right hemisphere function. Performance on the Wisconsin Card Sorting Task, a test which is sensitive to frontal lobe impairment was normal, however.

Clinical memory tests

E.L.D.'s performance on the Wechsler Memory Scale revealed a memory quotient of 100. Since this score is somewhat lower than her Verbal IQ of 119, it is consistent with her complaint that, in general, her memory is not as good as it was before her illness. In addition, there is some evidence from the test breakdown presented in Table 1 that performance is not particularly good on those subtests that are most sensitive to episodic memory problems (e.g., Memory Passages and Paired-Associate Learning). Nevertheless, her score on these subtests was within 1 SD of performance by controls. As a consequence, these results as well as others which are presented below, make it clear that E.L.D. does not suffer from a general memory impairment.

Performance on Warrington's (1984) Recognition Memory Test revealed a striking pattern. On the test for words, E.L.D. scored 43/50, which is well within the normal range. This involves the subject being presented with 50 English words, followed by a recognition test in which each target word is paired with 1 distractor. The test for faces is similar except that unfamiliar faces are used as stimuli. Here, however, E.L.D.'s score was only 34/50, a level of performance which is over 2.5 SDs below the mean for her age group. The difference of 9 between performance on the two tests is also extremely large—only 5% of Warrington's control sample has a higher discrepancy between their scores on the two tests than this. When retested 2 yrs later, she showed an even larger discrepancy, scoring 49/50 on words and 29/50 on faces.

TABLE 1. E.L.D.'S PERFORMANCE ON THE WECHSLER MEMORY SCALE

Information	5/6
Orientation	5/5
Mental control	7/7
Digits	13/15
Memory passages	6/25
Visual reproduction	8/14
Paired-associate learning	11.5/21
Memory Quotient	100

As a result of E.L.D.'s impaired performance on this test, despite normal scores on recognition memory for words and on face matching tasks, and because of her spontaneous complaint of inability to learn new faces, a series of experimental investigations was initiated in an attempt to define the precise nature of the problems that she experiences in remembering faces. The first experiment sought to investigate the generality of the impairment in learning new faces by examining whether the deficit that had been revealed on the faces part of the Warrington Recognition Memory Test could also be observed in a different type of recognition memory test involving the detection of recurring unfamiliar faces.

Experiment 1

Methods

E.L.D. was shown a sequence of 8 black and white photographs, all of which contained the face of one young man. The faces were exposed for 3 s each. The instructions indicated that she should attempt to learn the faces since she would shortly be asked to pick out the faces that she had seen from a much larger set of unfamiliar faces. As soon as all the faces had been presented, the test phase began. A single-item recognition memory test was used in which the 8 target faces plus 12 distractor faces of young men not shown earlier were presented one at a time in random order for an old/new recognition memory decision. After this, the 8 targets were presented again, mixed with 12 new distractors for a further set of old/new decisions. Finally, the 8 targets were tested a third time in identical fashion with 12 new distractors. This test was kindly loaned to us by Dr Edward De Haan of the Radcliffe Infirmary, Oxford.

Results and Discussion

Table 2 provides details of E.L.D.'s performance on this test, together with the performance of 19 female control subjects of similar age and educational background. The performance of 3 male Korsakoff amnesic patients (average age 66 yrs) is also included for comparison. It is clear that E.L.D.'s performance is severely impaired relative to the controls, and that her overall sensitivity is as poor as that of the 3 Korsakoff patients. She achieved only 6 hits out of 24 on the task whereas only 4 of the 19 controls achieved less than 20 hits, with the lowest control score being 13. It is also interesting to note that although d' values (a measure of sensitivity in the recognition test) are similar, the Korsakoff patients achieved more hits at the expense of four times as many false positives as E.L.D. who gave few false alarms.

TABLE 2. E.L.D.'S PERFORMANCE ON A YES/NO RECOGNITION MEMORY TEST FOR RECURRING UNFAMILIAR FACES

	Hits	*False alarms*	*d'*
19 female controls	0.89	0.09	2.57
E.L.D.	0.25	0.08	0.73
3 Korsakoff patients	0.61	0.32	0.75

E.L.D.'s extremely poor performance on this task confirms the impairment that was evident from her faces score on the Warrington Recognition Memory Test. She finds it extremely difficult to remember new faces on both forced-choice and single-item yes/no recognition memory tests.

Experiment 2

In the second experiment, we examined E.L.D.'s ability to recognize famous faces and names. If she does suffer from a severe impairment in learning new faces, then it would be expected that she would also experience great difficulties in identifying the faces of celebrities who have become famous since 1985, the time of her illness. As her performance can be compared with her ability to recognize faces of people who became famous before 1985, this test provides an opportunity of investigating whether her problems are specific to new faces or whether she also finds it difficult to recognize previously well-known faces. In addition, since E.L.D.'s ability to recognize the names of these celebrities can also be examined, we have a further opportunity of assessing whether her difficulties are confined to visual rather than verbal long-term memory.

Methods

A total of 78 3.5×5 inch black and white photographs were assembled. Each photograph displayed a frontal portrait of someone's face. Of these, 26 faces were of people who have achieved prominence from 1985 onwards (e.g., Mikhail Gorbachev, Sarah Ferguson, Madonna, John Stalker, Mike Gatting) and 26 were of people who were well known before 1980 (e.g., James Callaghan, Frank Sinatra, Jimmy Connors, Gracie Fields, Rod Stewart). The remaining 26 photographs were of people who are not famous. They were arranged in random order and presented to the subject one at a time. The subject's task was to rate the familiarity of each face on a scale from 1 (totally unfamiliar) to 7 (highly familiar), then state the person's occupation and finally give the person's name. Two weeks after E.L.D. had performed this task, she was given the names of the same people (unfamiliar faces were replaced by invented names) and ask to rate them for familiarity and state their occupation.

Results and Discussion

E.L.D.'s performance on this task, together with the scores achieved by 10 female control subjects of similar age and educational background, are given in Table 3. This shows that she performs within the normal range on faces which were famous before 1980. The number of occupations that she knew and the number of names that she could recall were virtually identical to controls. The familiarity rating is slightly lower but this arises from E.L.D.'s occasional reluctance, in common with a small number of normal subjects, to award a score of 7 even to a face that she immediately names without hesitation.

On the other hand, E.L.D.'s ability to recognize faces of people who have become famous since 1985 is severely impaired. Familiarity ratings, number of occupations that were known and the number of names that could be recalled in response to the photographs were all over 2.5 SDs below the scores produced by the control subjects.

Table 4 summarizes E.L.D.'s performance in recognizing names, together with the scores for 10 different age and sex-matched controls. Familiarity ratings and the number of occupations that were correctly recalled by E.L.D. are very similar to those of the controls. This is true for all names, those which have become famous recently as well as those which were famous before 1980. The results show that her problems in remembering new faces generalizes to people that she sees in the media. Furthermore, her problems do not appear to affect retrieval of old faces from memory, suggesting that this is indeed an anterograde problem and not a retrograde one. The finding that her performance was normal with recent names confirms that her problems relate primarily to visual rather than to verbal memory.

Even though the scores presented in Table 3 suggest that E.L.D.'s ability to recognize famous faces from the past is normal, it might still be argued that she may be identifying them on the basis of some abnormal strategy. The point that brain-injured patients may sometimes achieve an apparently 'normal'

TABLE 3. E.L.D.'S ABILITY TO RECOGNIZE 26 FACES THAT HAVE BEEN FAMOUS SINCE 1985 AND 26 FACES THAT WERE FAMOUS BEFORE 1980

	Familiarity rating (1 – 7 scale)	*Proportion given correct occupation*	*Proportion correctly named*
Pre-1980			
E.L.D.	5.50	0.85	0.73
10 female controls	6.21	0.82	0.70
SD	0.46	0.11	0.19
Post-1985			
E.L.D.	2.44	0.27	0.19
Controls	5.52	0.70	0.53
SD	0.52	0.07	0.13
Unfamiliar faces			
E.L.D.	1.42		
Controls	1.62		
SD	0.43		

TABLE 4. E.L.D.'S ABILITY TO RECOGNIZE 26 NAMES THAT HAVE BEEN FAMOUS SINCE 1985 AND 26 NAMES THAT WERE FAMOUS BEFORE 1980

	Familiarity rating (1 – 7 scale)	*Proportion given correct occupation*
Pre-1980		
E.L.D.	6.38	1.00
10 female controls	6.76	0.96
SD	0.28	0.06
Post-1985		
E.L.D.	4.69	0.62
Controls	4.93	0.59
SD	0.95	0.18
Unfamiliar names		
E.L.D.	1.08	
Controls	1.65	
SD	0.15	

overall level of performance by abnormal means is a compelling one (Newcombe, 1979). One way of testing this would be to look at the time E.L.D. takes to recognize famous faces. An abnormal strategy should lead to unusually long RTs. There is, however, no evidence that this is the case. She was given the familiarity decision tasks involving faces and names used by Newcombe *et al.* (1989). Her performance on these was entirely normal. Responding by means of a voice key to slides back-projected on a screen, she took an average of 927 ms to classify as familiar each of 16 famous faces from the past, and 1123 ms on average to reject 16 faces of people who are not famous. She made only 1 error, a false positive, on the 32 trials. Ten normal controls of comparable age produced slightly longer mean RTs of 1121 (SD 221) ms to familiar faces and 1301 (SD 395) ms to unfamiliar faces, with an average of 0.6 errors (SD 1.6). She also performed at normal speed on a similar test of name recognition (mean of 966 ms per trial for famous names and 1309 ms for unfamiliar names). Control subjects had a mean of 1080 (SD = 164) ms to familiar names and 1297 (SD 200) ms to unfamiliar names. She made no errors on the 32 trails (control mean 0.1 errors).

One interesting further question that might be raised is whether E.L.D. would show an impairment on faces that became famous shortly before her illness. Patients with Korsakoff's syndrome appear to perform particularly badly in tests of retrograde amnesia on the decade in which their illness started (Albert *et al.*, 1979). In addition, the amnesic H.M., whose problems primarily occur with new learning, also appears to have a retrograde impairment covering the months leading up to his temporal lobectomy (Corkin, 1984). We have not tested this possibility formally with E.L.D. since it would be exceptionally difficult to find an appropriate set of faces, but can offer the following observation. One of the recently famous faces that we gave her to identify was that of the tennis player Boris Becker. His was one of the very few recent faces that she recognized immediately and named without difficulty. Boris Becker won his first Wimbledon title in July 1985, some 2 months before E.L.D., who is an avid watcher of Wimbledon on television, sustained her aneurysm rupture. Since Becker was virtually unknown to the general public before the summer of 1985, this finding is consistent with the view that E.L.D.'s visual memory problems do not have a retrograde component for the period leading up to her illness.

Experiment 3

There is an alternative explanation for E.L.D.'s ability to recognize the old but not the new faces at normal levels in Experiment 2. Table 3 shows that the control subjects rated the pre-1980 faces as more familiar than the newer faces and also knew their occupations and named more of them. It would therefore be possible to argue that E.L.D.'s problem occurs with faces which are relatively difficult to identify rather than with new faces per se. This possibility was examined in Experiment 3.

De Haan *et al.* (1987) and Hanley *et al.* (1989) have used a set of faces which include a high familiarity set (e.g., Margaret Thatcher, Harold Wilson) and low familiarity set (e.g., Lucille Ball, Max Bygraves). From the relevant normative data it is clear that these low-familiarity faces are harder to identify than the recent faces that were used in Experiment 2. They therefore prove an opportunity for investigating whether E.L.D. has problems with recent faces or with 'difficult' faces.

Methods

The procedure was exactly as for Experiment 2. E.L.D. was presented with a total of 60 black and white photographs of faces; 20 were of 'high-familiarity people', 20 were of 'low-familiarity people' and 20 were of people who are not famous. She was asked to provide familiarity ratings, state their occupation and provide their names.

Results and Discussion

E.L.D.'s performance in Experiment 3 is presented in Table 5, together with control data from 28 normal subjects tested at the Radcliffe Infirmary, Oxford. Two aspects of these data are of interest. First, compare the controls' ratings of the low-familiarity faces with those of the recent faces in Table 4. It is clear that the low-familiarity faces in Table 5 are rated as less familiar and slightly fewer of them can be identified by name or occupation. Secondly, it is equally clear that E.L.D. performs just as well relative to controls on the low-familiarity faces as she does on the high-familiarity faces. This would appear to exclude any explanation of her poor performance on recent faces in terms of their difficulty rather than their recency.

Experiment 4

The findings thus far indicate that E.L.D. has a problem in remembering new faces regardless of whether they are encountered in laboratory experiments or through the media. Conversely, she appears to have no problems in recognizing faces that she knew before her illness. The remaining experiments examine

TABLE 5. E.L.D.'S PERFORMANCE IN RECOGNIZING LANCASTER/RADCLIFFE FAMOUS FACES LINE-UP

	Familiarity rating (1–7 scale)	*Proportion given correct occupation*	*Proportion correctly named*
High-familiarity faces			
E.L.D.	6.30	0.95	0.85
Controls (n = 28)	5.98	0.94	0.81
SD	0.51	0.06	0.14
Low-familiarity faces			
E.L.D.	4.50	0.55	0.50
Controls (n = 28)	4.18	0.65	0.47
SD	1.02	0.23	0.06
Unfamiliar faces			
E.L.D.	1.60		
Controls (n = 28)	1.36		
SD	0.45		

whether she might perform better in laboratory tests of episodic memory when the stimuli are faces that she recognizes rather than faces that she does not. A test analogous to the Warrington Recognition Memory Test was therefore prepared which included famous rather than unfamiliar faces.

Methods

E.L.D. was presented with a series of 50 3.5×4 inch black and white photographs of famous people. These were presented for the same duration (3 s) as that used in the Warrington Recognition Memory Test. E.L.D. was asked to decide whether she found each face pleasant or unpleasant, and was told that her memory for the faces would subsequently be tested.

Following presentation of the faces, E.L.D. was given 50 test trials. On each trial, one of the target photographs was paired with a distractor face which was of a famous person that had not been seen earlier. She was asked to indicate which of the 2 people had been in the original series of faces. We will refer to this as the 'which person' test.

Once this test was complete, E.L.D. was given a further memory test which also comprised 50 trials. On every trial, she was shown 2 different photographs of each target celebrity and was asked to indicate *which photograph* of the celebrity she had been shown when the targets had originally been presented.

Results and Discussion

E.L.D.'s performance in Experiment 4 is presented in Table 6 along with the scores obtained by a postencephalitic patient B.D., whose problems in remembering people were reported by Hanley *et al.* (1989). B.D.'s score on the Warrington Recognition Memory Test was also low (30) but he experienced as much difficulty in identifying faces from the past as he did with people encountered since his illness.

It can be seen that E.L.D.'s performance in remembering these faces is extremely good, bearing in mind her severely impaired score of 34/50 on the Warrington Recognition Memory Test. Her score is very good when she is asked to decide which person she saw previously, but it is also suggestively high when she is asked to judge which view of the person she saw previously. Conversely, B.D. did not perform well on either test. His ability to remember the famous faces in the 'which person' test was much worse relative to E.L.D. than his performance on the unfamiliar faces. Although B.D.'s performance on the Warrington Recognition Memory Test was slightly lower than that of E.L.D., we subsequently had the opportunity of testing B.D. on the unfamiliar faces used in Experiment 1. On that test, he performed somewhat

TABLE 6. E.L.D.'S PERFORMANCE ON A RECOGNITION MEMORY TEST FOR FAMILIAR FACES, IN COMPARISON WITH POSTENCEPHALITIC PATIENT B.D.

	Which person?	*Which view?*	*Warrington Recognition Memory Test*
E.L.D.	47/50	42/50	34/50
B.D.	32/50	35/50	30/50

better than E.L.D. (d' of 1.13 compared with 0.73). Their ability to remember unfamiliar faces is therefore probably not very different. Consequently, B.D.'s poor performance with the famous faces in this task makes it unlikely that E.L.D. performs better in this experiment than in the Recognition Memory Test simply because the Recognition Memory Test is more difficult.

Experiment 5

Despite the points raised above, there are several ways in which the design of the test used in the previous experiment could be improved. It would be preferable to be able to match the similarity between the targets and the distractors in the set of famous faces and the set of unfamiliar faces. In addition, the test of which view had been seen could not be administered until some while after the initial presentation of the target stimuli. This was at a time when each target photograph had already been exposed to the subjects twice.

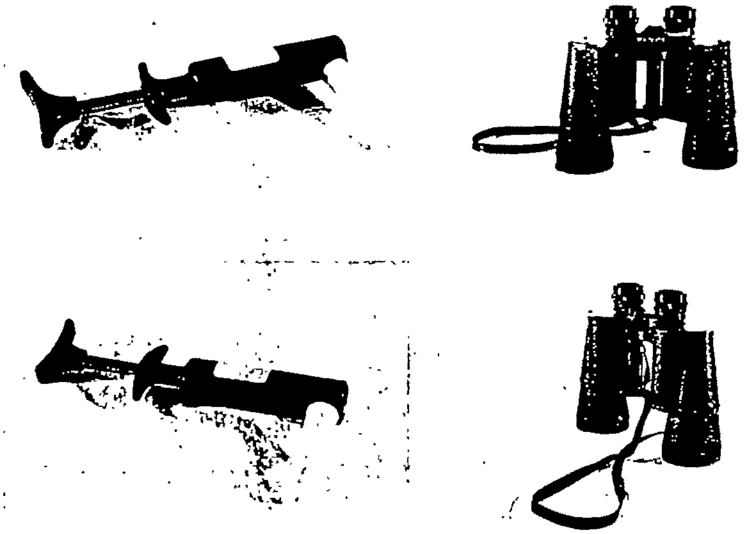
In Experiment 5, normative data concerning physical similarity between target faces and distractors were collected before the experiment began, and used to match the sets of faces chosen. In addition, an entirely separate recognition test investigated memory for which view had been presented. Memory for famous and unfamiliar faces was examined in the same test sessions.

Experiment 5 also incorporated a test of memory for familiar and unfamiliar objects. If E.L.D.'s superior episodic memory performance on familiar than unfamiliar faces is replicated in this experiment, it becomes important to ascertain whether she shows a corresponding pattern when the stimuli are photographs of objects rather than faces.

Methods

Four tests of recognition memory were prepared. Two of the tests used photographs of objects and 2 used photographs of people. In addition, 1 test of each type examined memory for which item had been presented and the other examined memory for which view of an item had been presented. Each test comprised 40 target items, 20 of which were familiar (famous faces or well-known objects) and 20 of which were unfamiliar (faces of people who are not famous and very unusual objects). In the test, the distractors were either a picture of another familiar or unfamiliar item ('which-time' test) or a different photograph of the same item ('which-view' test). Items for these tests were selected from a large pool of potential items that were rated on several characteristics by 6 independent judges. On the which-item test, if the target was a familiar item, then the distractor was also a familiar item, etc. The unfamiliar items achieved a mean rating of less than 1 on a 0–6 familiarity scale, whereas the familiar items were rated at over 5. The 6 raters also considered the familiar and unfamiliar objects to be equal in complexity. The ratings for differences in camera angle, difference in expression, difference in background, and difference in appearance between target items and distractors were also matched across the sets of familiar and unfamiliar faces. Examples of the stimuli used are shown in fig. 1.

Both E.L.D. and the controls performed the which-item test with objects first, followed by the which-item test with faces and then the which-view (faces) test. Presentation of the stimuli and the testing procedure were identical to those used in the previous experiment. E.L.D. received the which-view (objects) test a month later. There were two differences in procedure for the which-view test (objects). First, the target stimuli were back-projected as slides onto a screen during presentation, but testing was done using



Unfamiliar

Familiar

FIG. 1. Example of the familiar and unfamiliar objects used in the 'which-view' recognition memory test in Experiment 6.

photographs, as for the other 3 tests. Secondly, subjects were not forewarned about the nature of the recognition test in the which-view (objects) test, where all they were told was that their memory would be tested.

Results

The performance of E.L.D. on the which-item and which-view recognition memory tests is presented in Table 7 together with the performance of age and sex-matched controls. On the which-items test, performance by both controls and E.L.D. is close to ceiling. Nevertheless, E.L.D.'s performance is lower on the unfamiliar than on the familiar items, and was below that of the controls for the unfamiliar items only. Only 1 of the 10 control subjects scored as low as E.L.D. (16/20) on the unfamiliar faces, and none of the control subjects scored as low as she did (17/20) on unfamiliar objects.

Performance on the 2 which-view recognition memory tests is also presented in Table 7. Here, performance by control subjects appears to be well below ceiling and an unambiguous pattern emerges. E.L.D. performs just as well as controls on the familiar faces but is severely impaired (no better than chance) on the unfamiliar faces. On both tests, unlike the controls, she shows an extremely large discrepancy between performance on familiar and unfamiliar items. Her score on the which-view test for familiar objects is actually rather better than controls, so her good performance here certainly cannot be explained in terms of a ceiling effect limiting relative performance by the controls. Memory for unfamiliar items is once more poor on the objects tests, 2.4 SDs below controls ($n = 6$).

We have subsequently investigated E.L.D.'s ability to perform these 4 tests as simple matching tasks. She made no errors under these circumstances, confirming that her problems with the unfamiliar items are related to memory rather than perception; she can see the differences between the unfamiliar stimuli even though she does remember them.

It is clear that the pattern that was obtained in the previous experiment with E.L.D. has been replicated here. Once more, she is able to remember familiar items very much better than unfamiliar items whether

TABLE 7. E.L.D.'S PERFORMANCE ON RECOGNITION MEMORY TESTS FOR FAMILIAR AND UNFAMILIAR FACES AND OBJECTS

	Objects		*Faces*	
	Familiar (max=20)	*Unfamiliar (max=20)*	*Familiar (max=20)*	*Unfamiliar (max=20)*
Which item?				
E.L.D.	19	17	19	16
Controls	19.5	19.9	19.7	19.1
SD	0.67	0.30	0.64	1.45
Which view?				
E.L.D.	20	13	16	10
Controls	17.0	17.2	16.3	16.7
SD	2.30	1.72	2.57	1.55

the test involves memory for which item or which view was presented, or in addition, the findings of this experiment show that she performs in similar fashion whether the tests require memory for faces or memory for objects.

It is important to consider whether or not E.L.D.'s performance with familiar items in the which-view recognition memory tests could be based on verbal rather than visual coding. Might she, for instance, remember a *view* of Mrs Thatcher simply by coding it as one in which she is 'looking to the right, with a frowning expression'? We think not for four reasons. First, she denied such a strategy. Secondly, her performace was as good as that of normal subjects, whereas it might be expected that verbal coding would be of some assistance, but not to be as effective as the visual codes that normal subjects can use. Thirdly, E.L.D. performed normally on remembering views of familiar visual stimuli even when she was not informed as to the nature of the subsequent recognition test (in the which-view objects test). Fourthly, the differences between several of the pairs of items in the memory test phases of the which-view tasks were slight (*see* fig. 1), so that verbal coding could not be effective. We therefore consider her normal recognition of previously presented *views* of familiar objects and faces to be based on genuine visual memories.

Further discussion of the implications of these findings will be postponed until two final experiments involving recognition memory for verbal material and voices have been reported.

Experiment 7

So far, it has been demonstrated that E.L.D.'s impairment on recognition memory tests applies to unfamiliar rather than familiar faces and objects. The findings raise the possibility that she might perform badly on all tests of recognition memory that involve unfamiliar stimuli rather than tests which employ *visual* materials such as faces and objects per se. It will be recalled that E.L.D.'s good performance on the Warrington Recognition Memory Test was with familiar lexical items rather than with unfamiliar items. A test was therefore designed in which recognition memory for words and nonwords was compared.

Method

A total of 80 words (40 targets and 40 distractors) and 80 nonwords (40 targets and 40 distractors) were used in the experiment. All stimuli were taken from Ley and Karker's (1974) list of 5-letter CVCVC words and nonwords. Each target was matched with a distractor of equal pronounceability according to Ley and Karker's ratings. All 80 target items were typed in lower case on index cards and presented one at a time for 3 s each. E.L.D. was asked to decide whether each letter string represented an English word that she knew. At recognition, she was presented with 80 index cards one at a time in random order and was asked to indicate the target item. Forty of these cards contained 1 of the target words together with a distractor word, and the remainder contained a target nonword and a distractor nonword.

Results and Discussion

E.L.D. scored a total of 35/40 on recognition memory for the words and a total of 31/40 on the nonword items. Both these scores are very similar to those obtained by 5 matched control subjects who scored an average of 36/40 (SD = 2.61) on the words and 31/40 on the nonwords (SD = 3.03). It is therefore clear that E.L.D. does not suffer the same difficulties in remembering unfamiliar words that she encounters with unfamiliar faces and objects. This is further evidence that her memory problems are primarily with visual rather than verbal memory. Incidentally, her performance was perfect on the lexical decisions.

Experiment 8

The final experiment examined recognition memory for unfamiliar voices. If E.L.D.'s problems are confined to *visual* memory, then we would expect her to learn voices as easily as she learns words, nonwords and names. It is by no means certain, however, that this prediction would be correct. In a review of studies which have examined memory function following removal of the right temporal lobe, Milner (1974) concluded that memory for auditory as well as for visual patterns was impaired. On the other hand, Ross (1980) reported that, for 1 of his patients, auditory memory 'tested with noises and melodies' revealed 'no demonstrable difficulties' (p. 195). Unfortunately Ross provided no further details as to the nature of these tests and only appears to have examined auditory memory in the first of his 2 cases.

Methods

E.L.D. was asked to listen to a tape which contained 20 short sentences, each spoken by a different voice. Ten of the voices were male and 10 were female. The voices belonged to staff or students at the Univerity of Lancaster and were all unfamiliar to her and to the control subjects. She was asked to listen to the sentences and to pay particular attention to the voice, since memory for the voice would subsequently be tested. Examples of the sentences used were 'The cows were lying down in the field' and 'In autumn the leaves fall off the trees'. There was a 5 s gap between the presentation of each sentence.

When all the sentences had been presented, there was a few seconds delay while instructions were given before the recognition memory test began. On the test tape, each sentence was repeated, spoken by the same voice as before and also spoken by a new voice of the same sex that had not been heard previously. On half the trials the new voice came immediately before the old voice, and on the other the new voice came immediately after the old voice. As soon as the second sentence of each pair had been presented, the subject had to indicate which of the 2 voices had spoken the sentence originally. Subjects were allowed as long as they liked to make each decision.

Results and Discussion

E.L.D. correctly recognized only 11/20 of the voices. This compared with a mean score of 15.17 obtained by 6 matched control subjects (SD 1.07). Her score therefore shows clear signs of impairment on this task, being over 3 SD below controls. To discover whether her poor performance applied to familiar as well as unfamiliar voices, she was subsequently given the test for famous voices devised by Meudell *et al.* (1980). This comprises short extracts of famous voices from the 1930s to the 1970s. E.L.D. performed normally on this task, successfully naming 33/80 of the voices in comparison with the 37.6/80 voices (SD 13.72) named on average by the control subjects of Meudell *et al.* As is the case with visual material, E.L.D.'s problems in remembering voices occur only with unfamiliar items.

There would appear to be two possible interpretations for E.L.D.'s poor performance in recognizing unfamiliar voices. The first is that it has come about as a result of the same functional impairment that has led to her loss of recent visual memory. It this is true, then it might be better to think of her condition as involving not so much isolated loss of recent visual memory as isolated loss of recent nonverbal memory. The alternative interpretation is that her poor memory for voices is caused by an impairment that is quite distinct from the one that is associated with her poor memory for visual information. The second interpretation would be consistent with the views of Ross (1980, 1982). Investigations of memory for voices in other patients with loss of recent visual memory should help to clarify the situation.

GENERAL DISCUSSION

We have established that E.L.D. does not suffer from a general memory problem, and that she can learn verbal materials (words, pronounceable nonwords) normally, even when these are presented in the visual modality. She does, however, show a severe impairment of ability to learn new visual stimuli such as objects and faces. In contrast, her ability to recognize objects and faces that were familiar to her before her illness is unimpaired both in terms of overall accuracy and speed of response. Moreover, she shows normal recognition memory for previously familiar objects and faces, even when the memory test involves determining which of two views of the same object or face was previously presented. Hence it is only her memory for unfamiliar visual stimuli that is affected, producing the subjective complaint that even though she cannot recognize the faces of people she has met since her illness, she does know who these people are.

In establishing this description of E.L.D.'s problems, we have excluded several possibilities. Thus we demonstrated that her problem is not a general one involving recognition memory for any unfamiliar stimulus, since she had no difficulties with pronounceable nonwords. It is also clear that her problem is primarily one of memory rather than perception, since she has no difficulty in matching the stimuli that she remembers poorly if they are presented simultaneously. In addition, we do not consider that her normal learning of specific views of familiar objects and faces (in the which-view recognition memory tasks) can be based on use of 'verbal' coding, since a number of the pairs of views used were highly similar, and since normal learning of specific views was found even when she was not informed of the nature of the subsequent recognition test.

Finally, we have demonstrated that E.L.D. is not simply poor at recognizing faces of low familiarity. This is because she performs as well as normal controls at recognizing previously known faces of low familiarity, but performs worse than controls with recently encountered faces that are actually more easily recognized by (and more familiar to) the controls than are the low-familiarity faces. Her ability to recognize these low-familiarity items also makes it difficult to argue that she may have an impairment on premorbidly familiar items that is masked by ceiling effects in the performance of the controls. Control scores were well below ceiling on these items but she performed no worse than the controls. It is perhaps also worth pointing out that the absence of any difference between her and controls on familiar visual stimuli is of less theoretical significance than the very clear dissociation that she shows between memory for familiar and unfamiliar visual stimuli.

Although E.L.D.'s problems clearly involve a highly *selective* memory impairment, they were not exclusively visual. On a test of recognition memory for unfamiliar voices (Experiment 8), her performance was also impaired. As we have indicated, further studies of individual cases will be necessary to determine whether this association of visual and auditory (nonverbal memory) recent memory loss is coincidental for E.L.D., or reflects a more fundamental disruption to a system used in storing nonverbal memories.

Whatever the resolution of this particular question may turn out to be, our findings have important implications for understanding visual memory and its impairments. They extend the work of Ross (1980) and others, and demonstrate that a functional distinction should be drawn between verbal and visual long-term memory systems, and that retrieval of old visual memories can proceed normally even when the ability to remember new visual information is severely impaired. In addition, they demonstrate that cases of what Ross (1980) called visual recent memory loss need not involve impairment of *all* recent visual memories. Instead, the which-view tests demonstrate that E.L.D.'s visual recent memory is normal for familiar stimuli.

To understand the implications of this result, it is useful to distinguish between the structure of a visual *form*, such as an object or a face, and a specific *instance* of that form, such as a particular photograph. This distinction is similar to that made by Bruce (1983) and Bruce and Young (1986) between structural (form) and pictorial (instance) codes. Once the distinction is made, it is easy to see that E.L.D. can recognize forms that were familiar to her before her illness, and that she can store and retrieve new instances of these previously familiar forms, but that she cannot remember new visual forms, or instances of new forms.

Obviously, when we recognize familiar faces or objects in our daily lives we are continually having to recognize new instances of these known forms, because angles of view, lighting and so on are very variable. What E.L.D.'s case demonstrates, however, is that the *storage* of these new instances seems to be intimately linked to the operation of the recognition system itself, since she continues to be able to remember newly encountered instances of forms that she is able to recognize. This is consistent with the findings of a recent study of normal subjects by Ellis *et al.* (1987*b*), who found that repetition priming of familiar face recognition is sensitive to the instances (i.e., the particular photographs) used to prime recognition.

The point is worth emphasizing. A number of contemporary theoretical models of object and face recognition have been based on the notion of 'recognition units' (e.g., Seymour, 1979; Hay and Young, 1982; Warren and Morton, 1982; Bruce and Young, 1986; A.W. Ellis and Young, 1988). These models claim that recognition of a familiar visual stimulus involves matching the appearance of the seen object or face against a set of recognition units on the basis of visual features which they both share. Each recognition unit is considered to be maximally responsive to a particular familiar form. In some ways E.L.D. supports this type of conception, since she seems to be able to access recognition units established before her illness, but unable to create new ones. However, the recognition unit theories also make the assumption that these units operate in a purely 'abstractive' way, namely, that they do not store any record of the previously encountered instances of each form. On this assumption, E.L.D.'s ability to remember instances of previously familiar faces would have to be attributed to a separate 'pictorial' memory system. Yet such a pictorial memory system should also be able to store instances of unfamiliar faces, which is what she is unable to do. Hence it is more plausible to consider her ability to remember instances of familiar forms as reflecting the intact operation of previously established recognition units, which would imply that the 'abstractive' view of the operation of recognition units needs to be modified to one that is more instance-based. In such a conception, a memory trace for the particular view of a seen familiar object or face would be established automatically as part of the operation of the recognition system.

E.L.D., then, shows intact operation of face and object recognition units established before her illness, and severely impaired ability to establish new recognition units for faces and objects that are currently unfamiliar to her. Her case thus provides additional evidence of a difference between the processing of familiar and unfamiliar faces, a position previously adopted by Benton (1980) on entirely different neuropsychological grounds. It is notable, however, that the nature of E.L.D.'s impairment is clearly the same for both face and object processing. She shows a highly circumscribed deficit of memory for unfamiliar visual stimuli, but it is not specific to faces or objects as a stimulus class. Studies of other types of recognition impairment have tended to suggest functional differences between face and object processing (Young, 1988; H. D. Ellis and Young, 1989), and it will thus be interesting to see whether or not studies of other cases of impaired visual recent memory will produce specific impairments affecting either unfamiliar face or unfamiliar object memory.

E.L.D.'s normal performance on the 'which-view' test of recognition memory for familiar objects has an additional interesting implication. The objects used in the test were familiar *types* of object (shoes, cups, etc.), but the specific *exemplars* of each object were not chosen to be personally familiar to her. In other words we did not use *her* shoe, or *her* cup, in the memory task; rather it was someone else's shoe, etc. In fact it was most unlikely that she would ever before have seen a shoe, a cup, etc., that was *exactly* like those chosen for the experiment. Hence she is not only able to remember which photograph (i.e., which instance) of a previously familiar visual form that she has been shown, but she can also do this even when the photograph is of an item which is a previously unseen examplar of that form.

Our investigation of E.L.D. has demonstrated, then, that isolated loss of visual recent memory is a more subtle problem than it might at first appear. In essence, it seems to involve (at least for our case) impaired ability to make unfamiliar visual stimuli become familiar, leading to a marked dissociation in recognition memory performance to instances of unfamiliar and previously familiar visual forms. This has important implications for our understanding of visual memory and visual recognition, and demonstrates the potential value of applying the single case method favoured by cognitive neuropsychologists to different types of recognition impairment.

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MOVEMENT VARIABILITY AND BRADYKINESIA IN PARKINSON'S DISEASE

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SUMMARY

When making discrete aiming movements, patients with Parkinson's disease show greater inherent variability in the endpoints of their movements than do normal subjects. Endpoint variability can be reduced, by moving more slowly, by utilizing visual guidance, and by making small amplitude movements. The greater variability of patients is not a universal finding, but depends on the conditions of movement. For small movements the performance of patients equates to that of controls. For larger movements the results indicate that if sufficient time is available, patients can use visual guidance (if available) to reduce the variability of their movements to the level of normals. Patients can generate fast and/or large amplitude arm movements if required, but they are erratic if made in the dark or over a short duration. Their difficulty lies not so much in the magnitude of muscle force available to them, but rather in an inability to produce it consistently for any given movement attempted. Bradykinesia may in part result from this inherent variability in that parkinsonian patients, in order to maintain accuracy within acceptable limits, are forced to increase the duration of their movements to a level where they can make use of visual guidance. In any event, theoretical explanations for the movement disorder in Parkinson's disease advanced in the literature need to take some account of this increased variability of movement.

INTRODUCTION

The impairment of voluntary movement in Parkinson's disease (PD) is characterized by akinesia (slowness in initiating movements), hypokinesia (reduced amplitude of movements) and bradykinesia (slowness in executing movements). Studies by Flowers (1975, 1976) and others have shown that the course of parkinsonian movement is different from that of normals, with a lower initial acceleration, lower overall velocity, and less accuracy in most movements and particularly in larger amplitude ones. Parkinsonian subjects appear not to produce discrete 'ballistic' movements as normal subjects do. In producing fast accurate movement they do not seem to vary acceleration and velocity appropriately to comply with task demands. Moreover, they are dramatically affected by having to execute movements without visual information, as if they are more dependent on 'on-line' visual guidance to achieve a target.

Although a number of explanations have been put forward to account for these features, the most popular and simplest has been that of Hallett and Khoshbin (1980), who suggested that although the form of the muscle activity (in terms of the triphasic sequence of agonist-antagonist-agonist contractions) is normal in parkinsonian patients, the force generated

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is defective. Specifically, they suggested that patients do not vary appropriately the amount of energy put into individual movements of different amplitude, but produce the same, rather weak, force for all their actions. This means that while small movements can be executed reasonably well, larger ones require more than one sequence of the muscle 'program' to cover the distance.

As in Hallett and Khoshbin's account, if patients are exerting a constant weak force in all their actions it could explain both akinesia and bradykinesia, since it would be reasonable to assume that there would be an increased delay before the start of the movement became apparent and the acceleration and overall velocity of movement would be less than in normal movements. Hypokinesia would also result if the energy available to the system 'ran out' before the movement was completed, as it might well do if the initial amount applied to the movement was low. Other parkinsonian symptoms such as a tendency to fatigue quickly (Schwab and England, 1958) and general immobility (lack of spontaneous activity) might also follow from a simple difficulty in generating sufficient muscle force for voluntary actions.

There are, however, a number of difficulties with this account. In a previous investigation, Sheridan *et al.* (1987) found that parkinsonian akinesia was not simply a function of the amplitude of movement, but rather of the contingencies of its initial programming. Patients were slower than controls to initiate movements in a simple reaction time (SRT) condition where they had advance warning of the parameters of the movement, but not in a choice reaction time (CRT) condition where they did not. In the study of Flowers (1976) it was found that while patients were overall less accurate than controls, particularly in larger movements, they were also more variable and accuracy was related to the duration of the movement. In other words, patients could sometimes generate movements in a ballistic fashion, but if they lasted less than one visual reaction time in duration they tended to be very erratic. Patients thus had to make a trade-off of speed against accuracy; to go at a normal speed and risk a large error, or go more slowly and remain reasonably accurate. Finally, the disruption of movement with the loss of visual feedback about either the target or the hand movement (Flowers, 1976) cannot be explained solely in terms of force put into the movement. Movements should be the same with or without feedback if the deficit is simply in the force involved.

An alternative explanation for the impairment in voluntary movement in PD is that, while subjects can produce enough force to execute large amplitude movements, they cannot program it accurately. Thus movements of more than a minimal amplitude are liable to go astray as the force put into them varies from trial to trial in an unpredictable and erratic fashion, so that the patient cannot be sure where the arm will be at the end of a movement. Where subjects are unable to predict where their limb will be, they are forced to monitor each action while it is being made and put in secondary corrections using visual guidance so as to make individual movements accurate. If so, the accuracy of movement will be determined partly by the amplitude involved (larger movements allowing greater scope for variability), by the duration of movement, and by the availability of visual guidance. Where it is available and movements are sufficiently slow for it to be used to correct the endpoint of the movement, accuracy should be high.

But where it is not available, or movements are too fast for subjects to have time to make use of it, accuracy should be substantially less (i.e., greater variability of movement endpoints) in patients than in controls.

Following a previous study (Sheridan *et al.*, 1987) which suggested that increased variability of movement is an important factor in the motor dysfunction of PD, this investigation tested the hypothesis that movement variability would be significantly greater in parkinsonian patients than in controls, both for movements made in the dark, where no visual feedback was available, and for movements made over a short duration in the light, that is, where visual feedback was available but movements were too fast for it to be fully utilized.

METHODS

Subjects

Parkinsonian subjects were all from outpatient clinics at Hull Royal Infirmary and had a history of the disease lasting from 3 to 31 yrs. The patients, comprising 9 male and 1 female, were aged between 55 and 75 (mean 65.4, SD 7.2) yrs. Each patient was rated independently by Dr I. Pearce at 6-monthly intervals on the Webster scale of symptom severity and clinical disability (Webster, 1968). They all fell into the mild or moderate range of severity and were stable on individual drug regimens at the time of testing. The patients were not over-medicated and hence dyskinetic. Details of symptoms and treatment are shown in Table 1. Patients were tested on a 'good' day and time to minimize any possible effects of fluctuation in clinical state.

The Control group was drawn from a pool of local volunteers. The subjects (9 males and 1 female) were aged between 62 and 77 yrs (mean 69.2, SD 4.8 yrs), and they had no reported history of neurological problems. None was taking any drug that affected the CNS.

Informed consent was obtained from each subject to take part in the study. All patients and controls were right handed and they used this hand to perform the task.

Apparatus

The subject was seated in front of a Summagraphics digitizer with an active tablet area of 76 × 102 cm. On the horizontally orientated digitizer was fixed a matt black acrylic sheet with a single target line (20 cm in length) and 3 starting locations marked in yellow. The 3 starting positions were indented to facilitate location of the stylus. The seating arrangement was such that the target line coincided with the sagittal

TABLE 1. CLINICAL ASSESSMENT OF DISABILITY IN THE PARKINSONIAN GROUP

Case	*Age (yrs)*	*Webster score*	*Duration of illness (yrs)*	*Tremor (0–3)*	*Rigidity (0–3)*	*Bradykinesia (0–3)*	*Social disability (0–3)*	*Drugs*
1	61	9	6	2	2	2	1	Orphenadrine
2	61	11	8	2	1	1	0	Sinemet
3	67	5	3	1	1	1	0	Madopar
4	58	4	4	2	1	1	0	Orphenadrine
5	68	6	31	2	1	1	0	None
6	55	11	11	1	2	1.5	1	Sinemet, orphenadrine, Symmetril
7	73	12	7	2	2	2	2	Sinemet
8	61	10	6	2	1	2	1	Sinemet
9	75	9	5	2	1	1	0.5	Benzhexol
10	75	9	4	1	1	1	0.5	Madopar, orphenadrine

plane of the subject's body and was at right angles to the plane of movement (*see* fig. 1). Subjects received information concerning parameters of the impending movement on a monitor screen placed at eye level 100 cm in front of them. The monitor was also used to provide knowledge of results (KR) about movement time after completion of the movement. With their right hands, subjects held the digitizer stylus (which was 15 cm in length) and used this to make the movements. The imperative stimulus for movement was a 1000 Hz tone. Accuracy of the movement was recorded to within 0.1 mm by the digitizer. The only light source for the experiment was a fast decay fluorescent tube placed parallel to and forward of the plane of movement (*see* fig. 1). When turned off, the light source decayed to 10% luminescence within 10 ms. Data collection and control of the experiment proceeded automatically under computer guidance.

Procedure

The present study was designed to measure accuracy of arm movements on a task which required aimed movements at a target. The basic task required right-handed subjects to move a stylus leftwards from a given peripheral starting position, to a target line located directly in front of them. Subjects were instructed to hit, or get as close as possible to, the target line, within a criterion time. A target line rather than a zone target was used because interest was in variability of stopping (which involves variability in the forces of movement) rather than in errors concerned with directional biases from the starting position.

In a balanced design, 10 parkinsonian patients and 10 control subjects made movements over two movement times (300 and 1200 ms), of three different amplitudes (5, 15 and 30 cm), with or without visual feedback; a total of 12 conditions for each subject. The nesting of factors in the balanced design was such that movement duration was the slowest cycling factor (i.e., all fast movements were made first then all slow movements, or vice versa), then movement amplitude, and finally presence or absence of visual feedback was the fastest cycling factor. The order of conditions was yolked between patients and controls. In each of the 12 blocked conditions subjects made 5 practice movements followed by 10 test movements. Before each movement subjects received on the monitor screen information concerning the parameters of the impending movement; whether it was to be short (300 ms) or long (1200 ms) duration; short (5 cm), medium (15 cm) or long (30 cm) amplitude; and whether visual feedback was available or not. Thus for a sequence of 5 practice and 10 test movements the same information was repeated. The experimenter also monitored the information and provided appropriate verbal prompts to the subject. The instructions appeared for 5 s, after which, in their own time, subjects grounded the stylus on the digitizer at the appropriate starting location. This closed a microswitch in the tip of the stylus, and after a variable foreperiod of 1.5–2.5 s, the imperative stimulus (1000 Hz tone) sounded. Subjects were instructed to start the movement on detecting the imperative stimulus and to complete the movement within the criterion movement time, and to hit, or get as close

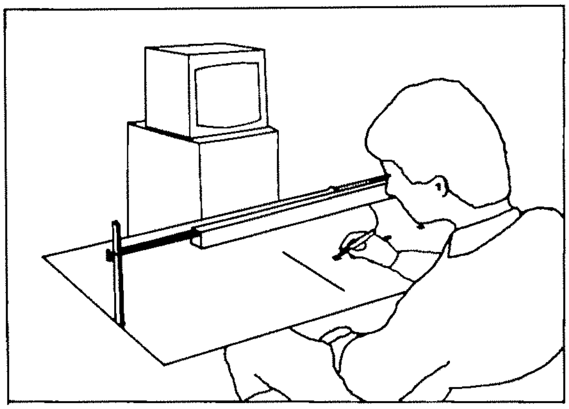

FIG. 1. Arrangement of the apparatus and subject.

as possible to, the target line. Response time was divided into reaction time (RT) and movement time (MT), although subjects were not aware of this. RT was the time from the imperative stimulus until the opening of the stylus microswitch, MT was from this point until closure of the microswitch on completion of the movement.

In the feedback condition the light source remained on during and after the movement. In the no-feedback condition, on starting the movement, the light was turned off and subjects completed the movement in the dark. On completing the movement by contacting the digitizer surface, the light was turned on again, and thus subjects were able to monitor their terminal accuracy, as in the feedback condition. On completion of the movement, KR about movement time was displayed on the monitor screen for 5 s. The subject was informed that the movement was 'too fast', 'o.k.', or 'too slow'. For the 300 ms condition, if the movement time was between 200 and 400 ms the subject was informed that the movement time was o.k., if less than 200 ms that the movement was too fast, and if greater than 400 ms that the movement was too slow. For the 1200 ms condition, the movement time o.k. message was displayed if the time was between 800 and 1600 ms, if less than 800 ms that the movement was too fast, and if greater than 1600 ms that the movement was too slow. Where necessary the experimenter provided appropriate verbal prompts. The cycle described was repeated for each movement.

Statistical treatment

Reaction time, movement time and movement accuracy data were analysed using analysis of variance.

RESULTS

Reaction time

Overall, there was no significant difference in reaction time (RT) between parkinsonian and control subjects (384 ms and 315 ms, respectively, F(1,18) = 2.29), nor any interaction between groups and conditions. This result reflects the constrained nature of response time in the present study, thus any differences between patients and controls were expected in the movement accuracy data. The pattern of the present RT data conform to that described by Sheridan (1984) and Siegel (1988). RT for the short duration condition was less than for the long duration condition with RTs of 285 ms and 415 ms, respectively (F(1,18) = 23.00, $P < 0.001$). There was no difference in RT between the visual feedback and no visual feedback conditions (340 ms vs 360 ms, F(1,18) = 2.87). There was, however, a difference in RT between the short (380 ms), medium (336 ms) and long (333 ms) amplitude conditions (F(2,36) = 6.53, $P < 0.001$). The only other significant effect was an interaction between movement duration and the presence or absence of visual feedback (F(1,18) = 8.28, $P < 0.025$). While the present study did not fractionate RT, the pattern of results supports the suggestion from studies which have (Sheridan, 1984; Siegel, 1988), that the rate and magnitude of force production, are important factors influencing RT.

Movement time

As movement time (MT) was one of the independent variables manipulated in the experiment, the data reported in this section provide an assessment of whether or not subjects complied with experimental requirements concerning movement duration. Overall, there was no difference in MT between parkinsonian and control groups (746 ms and 764 ms, respectively, F(1,8) = 0.54). Moreover, the factor of groups did not interact with any other factor (movement duration, movement amplitude, or visual feedback). Thus MTs were adequately controlled and equivalent in the two groups over all conditions so that the accuracy data for the parkinsonian and control groups are directly comparable.

The only significant MT effects were that short duration (300 ms) movements, not surprisingly, took less time than long duration (1200 ms) movements (F(1,18) = 825.53, $P < 0.001$), thus confirming the effectiveness of the manipulation of the independent variable of movement duration. The short duration movement with a mean target time of 300 ms actually took on average 371 ms, and the long duration movement with a target time of 1200 ms actually took on average 1139 ms. The only other significant effect was that subjects (both parkinsonian and control) were unable to maintain uniform movement time across different movement amplitudes (F(2,36) = 8.50, $P < 0.001$). Shorter amplitude movements were completed more quickly than longer amplitude movements (727, 756 and 782 ms, respectively). No other factors were significant.

Movement accuracy

To provide maximum information concerning subjects' performance, and in line with recommendations in the literature (e.g., Schutz and Roy, 1973; Schutz, 1977), movement accuracy is reported in terms of both constant error (CE) and variable error (VE). CE is the within-subject mean of the distribution of movement endpoints, and is a measure of individual bias. VE is the within-subject standard deviation (SD) of the movement endpoints, and reflects an individual's consistency of performance (scatter of shots about the target). Accuracy data are presented here as absolute numbers rather than as percentages of the desired movement length. The reason for this is that absolute magnitude of error is what has to be compensated for in the 'real world' in order to achieve a successful outcome, and thus this measure is more ecologically valid. In any event, the main interest is in comparisons between patients and controls, and since distance was equated the relative differences remain unaltered whether absolute numbers or percentages are used.

Constant error

In terms of CE, overall patients undershot the target more than controls (F(1,18) = 6.19, $P < 0.025$), with mean values of 6.4 mm and 0.9 mm, respectively. However, this effect did not interact with conditions (movement duration, movement amplitude, or visual feedback). The only modification to this pattern of results was that, for short duration movements, there was a noticeable trend in the data for the difference in undershooting between patients and controls to increase with increasing amplitude (F(2,36) = 3.22). This trend approached the conventional level of statistical significance. Other significant effects were that subjects (both parkinsonian and control) undershot more in the short duration condition (6.1 mm) than in the long duration condition (1.2 mm) (F(1,18) = 12.99, $P < 0.01$). Also, subjects undershot more in the no visual feedback condition (5.4 mm) than in the visual feedback condition (1.9 mm)

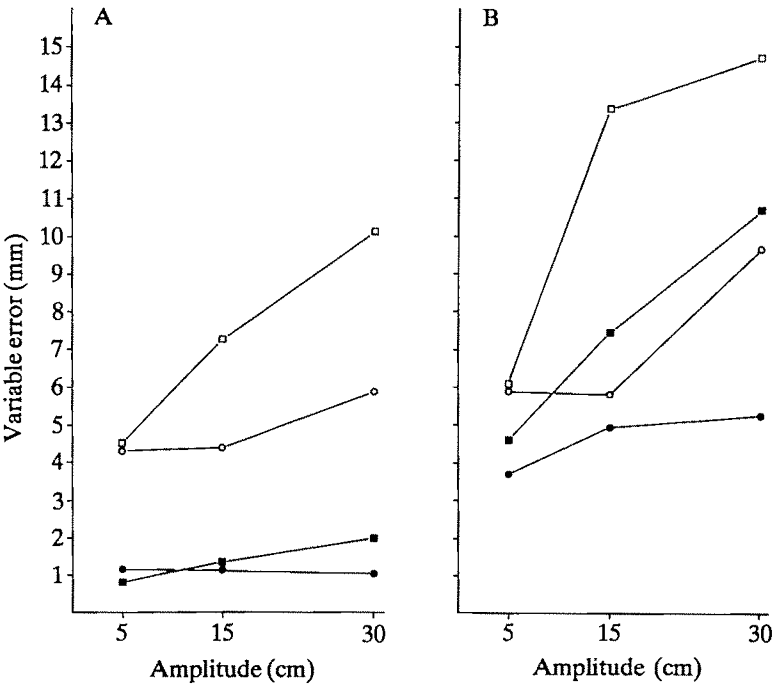

FIG. 2. Mean variable error as a function of groups, by amplitude, by duration. A, visual feedback; B, no visual feedback. Squares = parkinsonian patients (n = 10); circles = age-matched controls (n = 10). Closed symbols = long duration (1200 ms); open symbols = short duration (300 ms).

TABLE 2. COMPARISON OF VARIABLE ERROR SCORES BETWEEN GROUPS AT EACH LEVEL OF AMPLITUDE AND DURATION, WITH AND WITHOUT FEEDBACK

	Visual feedback (fig. 2A)			*No visual feedback (fig. 2B)*		
	Amplitude (cm)			*Amplitude (cm)*		
	5	*15*	*30*	*5*	*15*	*30*
Duration						
Short (300 ms)	F(1,9) = 0.01 n.s.	F(1,9) = 8.85 $P < 0.025$	F(1,9) = 8.13 $P < 0.025$	F(1,9) = 0.01 n.s.	F(1,9) = 6.84 $P < 0.05$	F(1,9) = 11.93 $P < 0.01$
Long (1200 ms)	F(1,9) = 0.17 n.s.	F(1,9) = 0.01 n.s.	F(1,9) = 0.87 n.s.	F(1,9) = 1.02 n.s.	F(1,9) = 3.42 n.s.	F(1,9) = 8.47 $P < 0.025$

(F(1,18) = 28.67, $P < 0.001$), and less in the short amplitude movements than longer amplitude movements (1.0, 4.6 and 5.5 mm, respectively; F(2,36) = 6.18, $P < 0.01$). The only significant interaction was between movement amplitude and visual feedback. Undershooting increased with increasing movement amplitude in the no visual feedback condition, while it remained virtually constant in the visual feedback condition (F(2,36) = 5.86, $P < 0.01$). No other CE factors were significant.

Variable error

For the VE data, overall there was a difference between the performance of patients and controls (F(1,18) = 7.34, $P < 0.025$) with mean values of 7.0 and 4.4 mm, respectively. In terms of main effects, short duration movements were more variable than long duration movements (F(1,18) = 53.2, $P < 0.001$) (7.6 and 3.7 mm, respectively); movements with visual feedback were less variable (3.7 mm) than movements without visual feedback (7.6 mm) (F(1,18) = 57.39, $P < 0.001$); and short amplitude movements were less variable than longer amplitude movements (4.0, 5.7 and 7.4 mm, respectively) (F(2,36) = 17.52, $P < 0.001$). In contrast to the CE data, for the VE data the differences between groups interacted with conditions. Differences between parkinsonian and control subjects interacted significantly with the availability of visual feedback (F(1,18) = 6.02, $P < 0.025$), with the amplitude of movement (F(2,36) = 6.57, $P < 0.025$), and with duration and amplitude of movement (F(2,36) = 3.5, $P < 0.05$). The source of the interactions can be seen in fig. 2.

Statistical comparisons between patients and controls for each level of the factors presented in fig. 2 are displayed in Table 2. As can be seen, for short movements (5 cm) patients were no more variable than controls, irrespective of feedback or movement duration (fig. 2). For longer movements (15 and 30 cm), parkinsonian subjects showed greater variability if either visual feedback was not available during the movement (fig. 2B), or movements were of short duration, so that less time was available for visual guidance (fig. 2A). The statistical exception to this description was that the difference between patients and controls at 15 cm for the long duration, no visual feedback condition was not significant (Table 2). For all movement amplitudes, if movements were of sufficient duration and visual feedback was available, parkinsonian VE was no greater than that of controls (fig. 2A).

DISCUSSION

As a consequence of the experimental design there was no overall difference between patients and controls in terms of RT. Moreover, for RT there was no difference between groups in any condition of movement duration, movement amplitude or visual feedback. For both parkinsonian subjects and controls, the pattern of the present RT data follow that described by Sheridan (1984) and subsequently confirmed by Siegel (1988), showing that rate and magnitude of force production are important factors influencing RT.

As expected, MT in this experiment was controlled in both groups so that there was no difference in MT between parkinsonian and control groups over any of the conditions of the experiment (duration, amplitude, and presence or absence of visual feedback). This allows the movement accuracy data for the parkinsonian and control groups to be compared directly as a measure of subjects' ability to generate precise movements. Therefore, any differences in performance between groups were expected to be expressed in the accuracy data. Consideration of movement accuracy is thus central to the present study.

The analysis of CE reveals that, overall, patients undershot the target to a greater extent than controls, reflecting the well-documented symptom of hypokinesia. This effect did not, however, interact with movement duration, movement amplitude or visual feedback. For *both* patients and controls undershooting was greater with short duration movements, with no visual feedback, and with longer amplitude movements. Thus, while for both groups the specific parameters of the movement affected undershooting, they did not affect the overall tendency for patients to fall shorter of the target than controls. This general description should, however, be tempered by a trend in the data present for short duration movements. With increasing amplitude (and hence higher velocity), the difference in undershoot between patients and controls increased.

A number of interpretations could be placed on the CE results.

1. That the greater undershoot in patients is caused by faulty perceptual processing and spatial awareness. This seems the least attractive possibility since the work of Brown and Marsden (1986) does not support the idea of a generalized visuospatial deficit in Parkinson's disease. Their subjects fell into the mild to moderate range of symptom severity which equates them with subjects in the present study.

2. That there is a general underproduction of the forces necessary for movement. This account has more than one version. In normal subjects, EMG shows a characteristic triphasic pattern of agonist and antagonist activity associated with rapid voluntary movement. Hallett and Khoshbin (1980) have shown that in Parkinson's disease the size of the first agonist burst is frequently insufficient to achieve the required force for a large fast movement. To compensate for the overall downward scaling of activation of the triphasic pattern, patients attempt rapid movements by a multistepping response involving repeated cycles of alternating agonist and antagonist activity. Contrary to previous suggestions (Hallett and Khoshbin, 1980), the deficit does not appear to arise from an upper limit on the size of the agonist burst since Berardelli *et al.* (1986) report that the amount of EMG activity does not saturate, but can be modulated, within limits, to the size of the movement required. So proportionality in the size of the agonist burst is maintained although it is inappropriately scaled to the movement amplitude and velocity. Patients in the present study were certainly able to move as quickly as controls, but at the cost of increased variability of movement. An alternative version of the hypothesis related to force underproduction has been advanced by Moore (1987). Here it is suggested that abnormalities of sensorimotor integration (e.g., reduced corollary discharge) could account for hypokinesia and bradykinesia in Parkinson's disease. With the demonstration by Wing (1988) that the deficit can be greater for force reduction, the area is clearly in need of some clarification.

3. That hypokinesia and bradykinesia could, in part, be a behavioural adaptation by patients to a motor system with inherently high variability. VE will be discussed in detail later. In normal life, when one does not know where an arm movement will terminate (i.e., high variability of movement) it is often better to be short of the target and approach it only slowly using visual guidance. For example, in picking up a glass of water, if one aims directly at the target, because of increased variability of movement, there is the chance of an overshoot and this can have the unfortunate consequence of knocking the glass over. For movements requiring accuracy, task demands may predicate

a strategy of undershoot in patients, with slow visual guidance to target contact. This need not be a conscious adaptation caused because patients are concerned that their movements are more variable than they expected them to be. They need not even necessarily notice the adaptations they are making, since adjustments take place over an extended period of time as the disease manifests itself and progresses. An analogy would be with a growing child that does not notice that it makes adjustments for the changing length and mass of its limbs.

Turning to the VE data, patients overall were more variable in performance than controls, confirming the observations of Sheridan *et al.* (1987). In an extension to previous work, and in contrast to the present CE data, the difference between groups for VE interacted with conditions. Differences between parkinsonian and control subjects interacted with the availability of visual feedback, with the amplitude of movement, and with the duration by amplitude of movement. The source of the interactions are displayed in fig. 2. As can be seen from fig. 2 taken in conjunction with the analyses presented in Table 2, for short movements (5 cm) patients were no more variable than controls, irrespective of feedback or movement duration. However, for longer movements (15 and 30 cm), in general patients showed greater variability than controls if either visual feedback was not available during the movement, or movements were of short duration, with less time available for visual guidance. For all movement amplitudes, if movements were of sufficient duration *and* visual feedback was available, the variability of parkinsonian movement was no greater than that of controls.

It could be argued that the reason patients are, in general, more variable than controls is that for any particular condition they are performing nearer to their maximum speed of movement than controls. There are a number of reasons against the idea that the effect is simply related to the percentage of maximum speed of movement. First, the argument holds less force for long duration (slow) movements, and yet, in the long duration, no vision, 30 cm condition, patients are still significantly more variable than controls. Secondly, for the short duration 5 cm conditions there is no difference in variability between patients and controls. Any difference in the groups' proximity to their absolute maxima would still exist here and according to the argument a difference in variability should exist, but in fact does not. Thirdly, in work by Sheridan *et al.* (1987) using an unconstrained movement condition (i.e., move without aiming at a target), even in a situation in which controls moved 45% faster than patients, patients were still significantly more variable. Here, if anywhere, percentage of absolute maxima would be more likely to be equated between groups. Thus it is considered that the variability effect is not simply related to the percentage of maximum speed of movement. What is observed is not an across the board difference between patients and controls, but one that depends on the conditions of movement. Furthermore, the variability displayed in parkinsonian movement does not seem to be related to the patients' tremor. Previous work (e.g., Flowers, 1975, 1976) has shown no evidence of parkinsonian tremor disrupting the end of a movement, unlike patients with essential or intention tremor.

The results of VE have implications for the various deficits suggested to underlie parkinsonian motor dysfunction, and discussion will now focus on this issue.

1. *Visuospatial deficit.* While the CE undershoot could potentially be explained in terms of a deficit in visuospatial performance, it is more difficult to account for the VE data in this way. For example, it is not clear, on this model, why reduced duration of movement should lead to significantly greater variability of movement in patients compared with controls. Moreover, the greater the potential involvement of visual guidance, the smaller is the difference in variability between patients and controls. This is not what one might expect if the deficit is primarily perceptual in nature, unless perhaps it lies in the kinaesthetic domain.

2. *Deficit in force production.* The common theme of the versions presented in the literature is that there is a general underproduction of the forces necessary for movement. The most well known version suggests that there is an overall downward scaling of activation of the triphasic pattern of agonist and antagonist activity (Hallett and Khoshbin, 1980). Recent work (Berardelli *et al.*, 1986) indicates that the picture is more complex and that EMG activity does not saturate, but can within limits be modulated to task demands. Patients in the present study were able to move as quickly as controls but, as indicated by the VE data, at the cost of increased variability. Increased variability of parkinsonian movement is an effect not directly predicted by, or dealt with, in current theories. In any event, reduced force production would, in normals, lead to predictions of *reduced* movement variability, and indeed this is what is found (e.g., Schmidt *et al.*, 1979; Newell *et al.*, 1982). Such predictions are based on the idea that impulses (forces applied over time, or force-time integral) accelerate and decelerate the limb. The size of the impulses (both amplitude and duration) determine where the limb will eventually stop, how rapidly it will travel there, and the spatial trajectory of the movement. Clearly, variability in the impulses will produce variability in the movement trajectory and/or in the movement endpoint. It is proposed that the magnitude of error in producing a force increases in proportion to the magnitude of force produced. Thus increases in movement distance or reductions in movement duration increase the force, which in turn increases force variability and leads to increased variability in the movement endpoints. The proposed relationship between movement amplitude (A) and movement time (MT) as they jointly affect accuracy, is given by the formula: $W_e = a+b$ (A/MT), with a and b as constants. Movement accuracy is measured in terms of the effective target width, W_e, which is the within-subject SD of the movement endpoints about their own mean. This is, in fact, the same as the VE term used in the present paper.

Abnormalities of sensorimotor integration (e.g., reduced corollary discharge) have also been advanced to account for hypokinesia and bradykinesia (Moore, 1987). Again, greater variability of parkinsonian movement does not figure in such an account. Models which propose a force deficit only in terms of force underproduction do not account for the greater variability observed in parkinsonian movement. Such variability in movement is presumably caused by variability in force production, but can be reduced if sufficient time is available to use visual guidance. Accounts of parkinsonian movement need to be based on models proposing more than a simple reduction in force production (e.g., Berardelli *et al.*, 1986), and the present results suggest that an understanding of force variability is critical to understanding the motor dysfunction displayed in Parkinson's disease.

3. *Adaptation to a motor system with inherently high variability.* While greater inherent variability in force production is likely to prove an important factor in the heightened movement variability observed in patients, it need not be the only factor. However, whatever the reasons underlying their more variable motor system, patients need to operate in the environment in such a way as to maximize the success of movement outcome. For tasks requiring some degree of accuracy it is necessary that patients reduce the endpoint variability of their movements. This is more critical for patients than normals in view of their greater inherent movement variability. The argument advanced is not that bradykinesia is caused solely by adaptation to variability, but rather that it is an important contributory factor.

Reducing variability can be achieved in a number of ways, and is akin to the type of speed/accuracy trade-off observed in normals. (1) Variability is reduced by moving more slowly (fig. 2B) and has been argued to be due to the reduced force impulse necessary for such movement when applied over a longer duration (Schmidt *et al.*, 1979; Newell *et al.*, 1982). The reduction in endpoint variability for movements made over longer durations occurs independently of the effects of visual guidance. (2) Movement variability is reduced by the use of visual guidance (fig. 2A). The effect is more pronounced if sufficient time is available to utilize visual feedback fully (i.e., longer duration movements). (3) Variability is reduced for shorter amplitude movements (fig. 2) and analysis reveals that there is no difference in movement variability between patients and controls for these short (5 cm) movements (*see* Table 2). Seen in this light, the occasionally observed 'shuffling' gait of patients involving small amplitude movements of the feet, might be an adaptation to avoid high variability in foot placement with the attendant disruption to fluid locomotion. Micrographia might also be a reflection of a similar process in the upper limb. The plausibility of this is increased by the finding that variability in force production is for individuals correlated across different effectors (finger, forearm and foot) and across low and high force ranges (Keele *et al.*, 1987).

In summary, endpoint variability can be reduced, by moving more slowly, by utilizing visual guidance, and by making small amplitude movements. The results indicate that if sufficient time is available patients can use visual guidance to reduce the greater inherent variability of their movements. Indeed the slowness of bradykinesia may be due in part to the need for patients to monitor their movements in order to reduce variability to an acceptable level, rather than simply an inability to generate sufficient forces. Thus bradykinesia may be a consequence of adaptation to the disorder rather than being the primary disorder itself. If so, any drug or other therapy attempting to ameliorate parkinsonian motor impairment will need to do more than simply energize the muscles or increase general levels of activity in patients; it will need to improve the patient's ability to control the forces generated in movement. Investigation of force production in PD would seem an important topic for future research. As suggested earlier in the discussion, hypokinesia, like bradykinesia, may be a consequence of adaptation to an inherently variable motor system; however, it probably also reflects movements being inappropriately scaled in terms of force. It is little wonder that in attempting to compensate for their more variable motor system, patients display a loss of coordination and fluidity of performance.

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PERCEPTUAL AND CONCEPTUAL MECHANISMS IN NEGLECT DYSLEXIA

TWO CONTRASTING CASE STUDIES

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SUMMARY

The contribution of peripheral, data-driven effects is contrasted with conceptual, 'top-down' effects to the reading performance of 2 subjects with neglect dyslexia following a single right hemisphere lesion. Several tasks were administered, manipulating the physical, lexical or morphemic properties of the stimuli in an attempt to establish whether the attentional deficit disrupts reading at an early or late stage of processing. Both subjects were impaired at detecting elementary stimulus features on the left side of the display but were even more impaired at identifying conjoined features. One subject's performance was influenced by structural manipulations which altered the low-level representation of the stimulus. The other was less affected by structural changes of the stimuli but was influenced by the lexical and morphemic status of the words. This apparent double dissociation is interpreted as arising from a graded attentional deficit at a single locus, early in the reading process where low-level information is detected. When the deficit is not severe sufficient information may be picked up and may interact with higher order lexical knowledge to offset partially the peripheral malfunction. For a severe attentional deficit, top-down knowledge is not engaged as insufficient information is processed on the left-hand side. This hybrid view of attention provides insight into the mechanisms underlying neglect dyslexia and bears on the role of attention in normal visual processing.

INTRODUCTION

Visual neglect following lesions of the right hemisphere in previously literate adults can result in reading impairments independent of aphasia. These impairments may manifest themselves in different reading tasks: the left side of an open book may be ignored, the beginning of lines may be omitted during text reading and/or the beginning letters of single words may be omitted (Friedland and Weinstein, 1977; Caplan, 1987). These deficits, which have come to be subsumed under the heading 'neglect dyslexia', were mentioned in several early papers (Gilliatt and Pratt, 1952; Kinsbourne and Warrington, 1962; Leicester *et al.*, 1969) but have received little in-depth discussion until recently. Evidence from the few detailed studies available remains contradictory with regard to the mechanisms underlying neglect dyslexia. While most people accept

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that an attentional deficit underlies the disorder, the nature of this impairment remains unclear. Heilman *et al.* (1985, 1987), for example, have argued that the brain lesion results in reduced arousal of one hemisphere. Sensory information which appears on the contralesional side is not adequately processed, giving rise to neglect. An alternative explanation put forward by Kinsbourne (1987) is that the attentional balance between the hemispheres is disrupted following a lesion. This produces a failure to attend to contralateral information, coupled with an exaggerated focus to the ipsilesional side. The outcome of this deficit is that a gradient of attention exists both within and across the visual fields. Consequently, for patients with right hemisphere lesions in whom the gradient provides more optimal attention on the side of the lesion, stimuli appearing on the right have a processing advantage, leading to left-sided neglect.

In order to understand better the nature of the attentional deficit following brain damage, several studies have set out to define the elementary operations of attention in relation to neural systems and then to relate these operations to processes such as visual pattern recognition (Posner and Presti, 1987; Posner, 1988; Posner and Petersen, 1989). The purpose of the present research was also to examine the role of attention in cognitive processing by investigating acquired neglect dyslexia in adults who were premorbidly literate. More specifically, the aim was to assess at what stage in the reading process the attentional deficit has its impact, namely, whether the disruption arises early or late in cognitive processing. Early disruption suggests that the impairment occurs before stimulus identification, that is, low-level representations are degraded or filtered. In contrast, late disruption implies that the attentional impairment plays a role once the stimulus has been processed to a high level and has been identified as a token of a specific category or type (Pashler and Badgio, 1987).

The issue of level of attentional selection has generated controversy for several decades in the cognitive psychology literature and continues to be of theoretical concern. The earlier literature on this issue reflected two opposing viewpoints, with Broadbent's (1958) early filtering theory at one end and the late selection theory of Deutsch and Deutsch (1963) at the other. Recently, it has been argued that early and late selection loci need not be mutually exclusive and a hybrid view of attentional selection has been proposed (Pashler and Badgio, 1987; Mozer, 1988). Evidence from neuropsychological studies on neglect dyslexia is pertinent to this ongoing controversy and may shed light on the attentional operations in normal visual spatial proccessing.

Proponents of an attentional disruption at peripheral stages of processing have attributed the deficit in neglect dyslexia to the abnormal distribution of visual attention in the early stages of reading. The left side of the stimulus is attenuated and registration of the features is impeded. Kinsbourne and Warrington (1962), for example, described 6 subjects with parietal lobe lesions who neglected the left side of words on bedside and tachistoscopic presentation and concluded that the reading disorder arises from 'a pathological alteration in perceptual processes' (p.344). This peripheral explanation is supported by V.B., a subject with neglect dyslexia (Ellis *et al.*, 1987), who produced a high number of left-sided neglect errors on words and nonwords. Since words and nonwords were equally affected, Ellis *et al.* (1987) concluded that the damage arose peripherally, before lexical status became a relevant factor and words made contact with their existing orthographic representations in the word-form system.

These peripheral explanations have been questioned by studies which have shown that neglect is not simply restricted to reading or to the visual modality but occurs across modalities. Several patients have been described who perform poorly on tasks such as oral spelling and/or writing (Baxter and Warrington, 1983; Barbut and Gazzaniga, 1987; Caramazza and Hillis, 1990). As errors are observed in different modalities, the deficit must arise in a mechanism which is common to all these modalities and which is centrally located at a high level in the processing system.

A further set of findings suggests that peripheral and central factors need not be mutually exclusive but may interact to produce neglect dyslexia. Several researchers have demonstrated that stimuli may be differentially affected depending on their lexical status. For example, some patients missed the first few letters of nonwords but not of words (Sieroff *et al.*, 1988; Brunn and Farah, 1990) or, for Chinese patients, neglected parts of pseudoideograms but not of genuine Chinese characters (Tzeng and Hung, 1989). Various explanations have been offered to account for the differential sensitivity of stimulus types. On one account, stimuli such as words or ideograms which have pre-existing lexical representations do not require the deployment of attention. Instead, they have privileged and direct access to their phonological and semantic codes (LaBerge and Samuels, 1974). Unfamiliar nonwords, on the other hand, rely on a serial attentional scan for readout of information and are, therefore, subject to the attentional disorder. An alternative account is that attention is always deployed, irrespective of stimulus type. When attention is disrupted, features of words and nonwords are not efficiently registered. The superiority of words over nonwords arises through interaction with 'top-down' knowledge. Words are boosted by their pre-existing lexical representations, which feed back down and enhance word perception (as proposed in the Interactive Activation Model of word recognition (McClelland and Rumelhart, 1981)). Because nonwords do not receive the advantage of such top-down support, they are more impaired. This latter interaction theory suggests that we cannot understand the attentional deficit solely in terms of peripheral factors since top-down processing may override a primary attentional disorder. While the primary problem is one of attention, its manifestation may be affected by stimulus variables such as lexical status. In these instances, neglect dyslexia reflects an interaction between a data-driven, bottom-up deficit and top-down, conceptual knowledge.

The peripheral or data-driven theory and the central, conceptual theory have dominated the neglect literature while less emphasis has been given to the interactive view. The study of reading and neglect dyslexia is potentially a valuable technique for understanding the mechanisms underlying neglect and for evaluating possible interactions. Written stimuli can be systematically varied along physical parameters (number, size and spacing of letters) to reflect bottom-up effects and along linguistic dimensions (lexicality and morphology) to demonstrate the operation of higher order top-down influences. Simply stated, if the attentional deficit occurs at an early stage, then performance would be affected by the physical dimensions or low level features of the stimulus. For example, words which have too many letters or are too widely spaced may be impaired relative to shorter words if the attentional 'spotlight' (Eriksen and Yeh, 1985) only illuminates a restricted region of space. If, however, the attentional disruption arises at later stages of processing, then we would predict that higher cognitive variables (such as lexical status or morphological composition) would influence subjects' performance since this information is accessed only at advanced stages of processing. Such predictions allow us to compare the contribution of data-driven bottom-up effects with top-down, conceptual effects and to examine combinations of early and late attentional selection in an interactive framework. In this study, we compared and contrasted the performance of 2 patients with neglect dyslexia on a number of experiments designed to test the above predictions.

CASE HISTORIES

Two subjects, both right-handed and English-speaking, demonstrated hemispatial neglect on bedside testing following a single right hemisphere stroke. Both subjects were mildly dysarthric and showed motor impersistence on lateral gaze and other actions. Neither subject demonstrated aphasia nor diffuse cognitive impairment consistent with dementia.

Case 1

H.R., a 61-yr-old male, was initially admitted to hospital in July 1986 with hemiplegia, left hemisensory loss and a left homonymous hemianopia. Before his stroke, he lived at home with his wife and was reported to be functioning normally. He was employed as a tinner in a steel and electronics plant but had held numerous other jobs in the past. He had completed 10 yrs of schooling. He was studied during a readmission to hospital in October 1987 for reassessment. At this time, he was still wheelchair-bound and exhibited a spastic left hemiplegia, significant left sensory loss and a complete left homonymous hemianopia on testing to confrontation with hand movements. He was mildly anosognosic, denying the extent and implications of his deficits. He scored 52 on a standardized stroke scale (Adams *et al.*, 1987) in which a score above 50 indicated a severe deficit. On the WAIS-R, H.R. had a low average full scale IQ with a verbal IQ in the average range and a performance IQ in the bottom twentieth percentile. His memory quotient on the Wechsler Memory Scale fell in the average range and was consistent with his verbal IQ score. His digit span was 6 forwards and 3 backwards. Speech was fluent, grammatical and without paraphasias. Auditory comprehension was normal. A CT scan in October 1987 revealed a patchy but extensive right middle cerebral artery territory infarct (*see* fig. 1, top row). At the time of testing, he was alert and cooperative and required minimal assistance in activities of daily living.

Case 2

A.H., a 70-yr-old male, was admitted to hospital in April 1987 and testing was initiated within 1 month of onset of his stroke. At the time of his stroke, he was a retired insurance agent who was an active member of the local golf club and was serving as chairman of its board. He had completed 13 yrs of formal schooling. His score on the Adams *et al.* (1987) standardized stroke scale was 28 (moderate 20–50). He had a complete left homonymous hemianopia on testing to confrontation with hand movement, and mild left-sided weakness and sensory loss, but was ambulatory. Standardized neuropsychological assessment 2 months after his stroke revealed marked impairment in visuomotor tracking (Trail Making test), constructional praxis (Rey-Osterreith Complex Figure) and visual-perceptual skills (Read Visual Closure test). On the WAIS-R, he had a low average verbal IQ, but his performance IQ was in the bottom tenth percentile. Performance on the Wechsler Memory Scale-Revised was impaired due to mild verbal and severe non verbal memory deficits. Left hemispatial neglect and decreased attention and concentration were evident throughout the testing session. A.H.'s CT scan revealed an infarct in the right middle cerebral artery territory involving the basal ganglia, deep white matter and the temporal and parietal cortex (*see* fig. 1, bottom row).

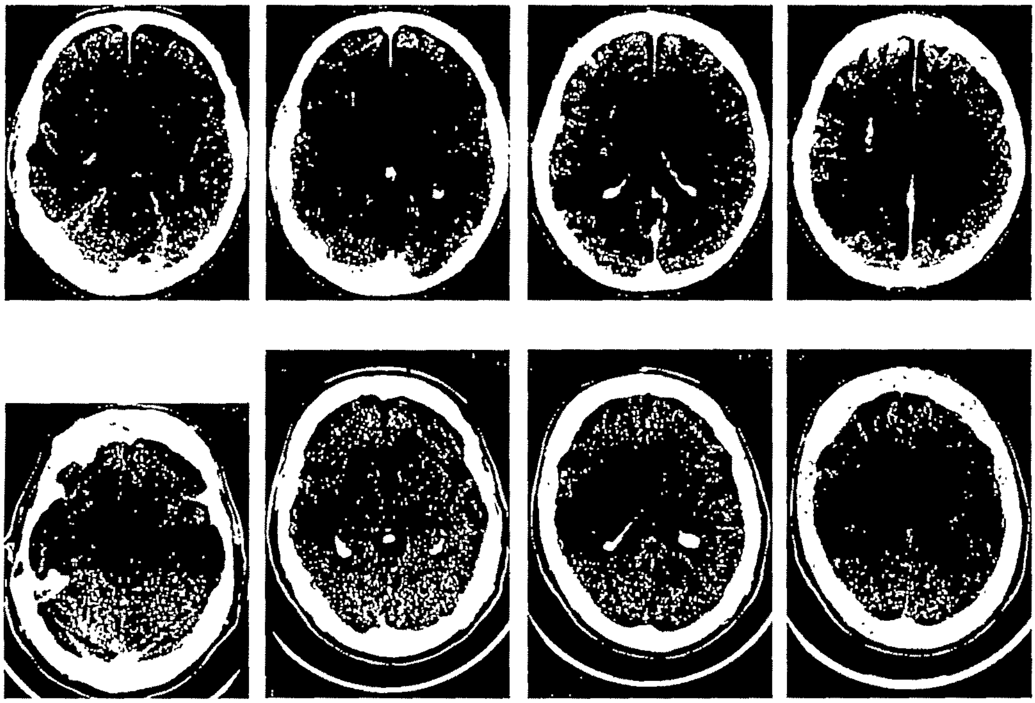

FIG. 1. *Top row*, CT scan for subject H.R. revealing a right middle cerebral artery infarct, involving the parietal and frontal areas, as well as the basal ganglia. *Bottom row*, CT scan for subject A.H. revealing right middle cerebral artery infarct, involving the basal ganglia, deep white matter and temporal-parietal cortex.

INITIAL INVESTIGATIONS

Bedside testing for hemispatial neglect

Both subjects demonstrated general left-sided neglect, not restricted to any one modality. All visual testing was carried out in the subjects' intact right field (neglect of the left-most stimulus within the intact field is often reported). On testing to confrontation with hand movement, H.R. and A.H. both showed extinction of the contralateral stimulus on double simultaneous stimulation in the intact visual field, a not uncommon finding which has previously been taken as support that neglect is not simply a product of a sensory disturbance (Gazzaniga and Ladavas, 1987). Extinction of the contralateral stimulus was also observed on auditory and tactile testing. Both subjects showed neglect on spontaneous drawing and copying of figures such as a daisy and a clock. The results of the line bisection, line cancellation (Albert, 1973), letter and symbol cancellation tasks (Mesulam, 1985) are presented in Table 1. Although both subjects exhibited severe neglect on bedside testing, A.H. performed particularly poorly. He only attended to the extreme right side and, therefore, omitted material even to the right of the midline of the page.

TABLE 1. RESULTS OF H.R. AND A.H. ON BEDSIDE SCREENING FOR HEMISPATIAL NEGLECT

Tasks	*H.R.* *(No. neglected)*	*A.H.* *(No. neglected)*
Line cancellation: 21 lines	11 on left 0 on right	7 on left 0 on right
Letter detection: 60 letters, ordered presentation	2 on left 0 on right	30 on left 15 on right
Symbol detection: 60 symbols, random presentation	15 on left 0 on right	30 on left 25 on right

Reading

Sixty single words of 3–7 letters in length and 60 matched pronounceable nonwords were presented individually in upper case to the subjects' intact right field on an Apple IIE computer for oral reading. The stimuli were presented horizontally on one occasion and then vertically on a second. Strings of 3–6 digits were also presented in horizontal format. Oral reading of text was assessed using Caplan's (1987) paragraph in which the starting position of the left-hand margin is varied from line-to-line.

There was no evidence of neglect on vertical words (accuracy 84% and 80% for H.R. and A.H., respectively) whereas performance on horizontal single word, text and digit reading, revealed a predominance of left-sided neglect errors. In addition to the within-word errors on Caplan's paragraph test, A.H. and H.R. both neglected left-sided information on 70% and 71% of the lines, respectively.

In an attempt to increase the corpus of errors for subsequent analysis, the horizontal words were re-presented to the subjects under limited viewing conditions. The subjects were trained to maintain central fixation and this was monitored using a video camera. Since A.H.'s performance remained unchanged with brief exposure, all subsequent testing was conducted under unlimited viewing time. H.R., however, produced many more errors at 500 ms and this exposure duration was selected for him for all further testing.

Cross-modality testing for central effects

In order to assess whether neglect was restricted to reading or whether it also affected other modalities, oral and written spelling were examined.

Spelling single words to dictation. Twenty high-frequency English words of regular and irregular orthography (3–7 letters in length) were dictated to the subjects for writing. A.H. wrote all words correctly. H.R. made 6 errors, a result which is in keeping with his educational background. For our purposes, it is relevant that none of the spelling errors involved the beginning or left-sided letters of the word.

Oral spelling single words. Fifteen high-frequency words (3–5 letters in length) were read aloud individually to the subjects for oral spelling. A.H. spelled all words correctly and H.R. spelled 11 words correctly. As in written spelling, no errors involved the left side of words.

These findings suggest that neglect of the left side of words does not arise at a central locus, common to all modalities. Instead, it is domain specific, affecting only words the subjects see, but not those they spell or write.

EXPERIMENTAL INVESTIGATIONS

Testing was carried out on a Macintosh Plus computer and 9 inch diagonal, high resolution, 512×342 pixel bit-mapped display screen using Psychlab software (Bub and Gum, 1988). In all cases, a central fixation point appeared 500 ms before the stimulus. Stimuli were presented in bold black 24-point font on a white background. All experiments were self-paced and responses were recorded manually for error analysis. Subjects were seated at a distance of 50 cm and the visual angle subtended by the stimulus was 2.3°, 3.4° and 4.6° for 3, 5 and 7 letter words, respectively.

Experiment 1: Manipulations of physical stimulus features

These experiments were designed to examine the effect of manipulating the physical dimensions of the stimulus on reading performance. If low-level manipulations such as stimulus orientation (horizontal *vs* vertical) or word length were shown to have an effect on performance, then we might conclude that the neglect dyslexia seen in these patients arises at an early stage of processing. Ellis *et al.* (1987), for example, showed that their subject neglected the left side of space (defined as left from the viewer's perspective) and was sensitive to the physical orientation of the stimulus. Performance on vertical words was superior to that of horizontal. Errors were made on the left side irrespective of whether the stimuli were presented in normal forward order (e.g., PLANE → 'lane') or backwards (e.g., LRAEP → 'pear'). These findings suggest that V.B.'s neglect arose at a low level of processing and was related to the left side of external space rather than to the left side of the internal representation of the word.

Preliminary evidence from our initial investigations suggested that our subjects' neglect was also operating with respect to the left side of space since performance was significantly better when the stimuli were presented in vertical rather than horizontal orientation. The following tasks were constructed to examine in more depth the influence of physical parameters of the stimulus on reading performance. The effect of stimulus extent in the horizontal plane was evaluated in two conditions. In one, length was altered by increasing the number of letters in the stimulus; in the other, the number of letters was held constant but the horizontal area covered by the stimulus was manipulated.

Number of letters

In order to evaluate the effect of stimulus length, a list of 210 words of 3–9 letters and 70 matched orthographically legal and pronounceable nonword foils was presented for oral reading. The mean frequency of occurrence was controlled across word lengths, ranging between a mean of 237 and 269 per million (Francis and Kučera, 1982). In order to minimize a possible lexical bias, the subjects were instructed that both words and nonwords would appear in the list. Table 2 shows the accuracy of report across the different word lengths. (Nonword foils were not analysed, but *see* Experiment 2 for investigation of role of lexical status on performance.)

H.R. read 65.1% (range 54–79%) and A.H. 75.3% (range 67–82%) of the words correctly. Word length did not have an effect on performance for H.R. ($r = 0.11$, $P > 0.5$) but a significant effect of length was seen in A.H.'s data ($r = 0.86$, $P < 0.01$) with reading accuracy decreasing as the number of letters increased. The majority of error responses contained approximately the same number of letters as the target word, suggesting that both subjects had some awareness of the stimulus length. In H.R.'s case, 67% of the errors were of the same length as the target and an additional 24% were either one letter longer or shorter than the target. Similarly, 53% of A.H.'s responses were of identical length to the target and all his remaining responses were either a letter shorter or longer than the target. A more detailed error analysis is provided later on.

TABLE 2. OVERALL READING ACCURACY FOR H.R. AND A.H. ACROSS VARYING WORD LENGTHS

Word lengths (no. of letters)	*Percentage correct*	
	H.R.	*A.H.*
3	79	80
4	55	82
5	67	76
6	54	75
7	70	77
8	62	70
9	69	67
Total	65.1	75.3

Discussion. These data indicate that the subjects differed in their sensitivity to the stimulus dimensions with A.H. being much more affected by word length than H.R. Both subjects, however, possessed rudimentary information about the length of the word, as indicated by the length of the error responses. These findings are consistent with the previous descriptions of patients who tended to substitute information on the left, thereby preserving word length (Kinsbourne and Warrington, 1962; Ellis *et al.*, 1987). From these results it appears as though A.H. was influenced by the physical features of the stimulus. It is not clear, however, whether the critical variable is the number of letters in the stimulus or the amount of horizontal space taken up by the stimulus since they are confounded in this task. Before considering why our 2 subjects were different, we attempted to separate out these dimensions.

Stimulus extent

In this experiment, the horizontal extent of the stimulus was varied independently of the number of letters. Two lists of words were constructed for oral reading and were run in two conditions. (1) Regular: 150 words of 3–5 letters were presented starting in the character space immediately next to the fixation asterisk (e.g., *ACE). The stimulus appeared 500 ms following the fixation point in the experiment; (2) Spaced: the same words were presented next to fixation but with a single character space between letters so that the visual angle subtended by these words exceeded that of the regular condition (e.g., *A C E).

There was no significant difference in H.R.'s performance across the two conditions (McNemar test n.s.), confirming the prediction that horizontal extent, produced either by increased letters or visual angle, did not influence his neglect dyslexia. For A.H., however, horizontal extent was a significant determinant of reading accuracy. Performance on the regular condition words was superior to that on the spaced condition (McNemar's test $\chi^2 = 6.8$, $P < 0.01$). An effect of increasing number of letters was also observed in the spaced condition: A.H. correctly read 77% of 3 letter words, 55% of 4 letter words and 33% of 5 letter words, confirming the previous finding of a word length effect. A.H.'s deterioration in performance with increasing horizontal extent was further confirmed in an additional manipulation. Words of 3–5 letters were presented immediately next to fixation but without a space between the letters. Instead, the letters were 'stretched' so that they covered the horizontal extent as the words in the spaced condition, for example, DOG. Performance on the stretched condition was not significantly different from that on the spaced condition (McNemar's test n.s.) but was significantly worse than that on the regular condition (McNemar's test $\chi^2 = 4.3$, $P < 0.05$).

Discussion. These findings demonstrate that H.R.'s neglect dyslexia was less affected by length manipulations than A.H.'s. A.H.'s sensitivity to various alterations of the physical parameters of the stimulus indicates that his attentional deficit impaired the extraction of low-level information from the left side of space. This was not the case for H.R.; although performance was not perfect, the attentional deficit did not prevent the stimuli from being processed at a higher level. An error analysis, consisting of errors produced in response to word and nonword targets, was conducted to provide further details about the information which the subjects were able to extract for later processing.

Error Analysis. The analysis (*see* Table 3) included the error responses from several experiments in which the regular presentation format was used and in which both subjects participated. This included experiment 1 (number of letters and stimulus extent) plus the near condition of Experiment 4 (discussed later)). A corpus of 101 errors for A.H. and 128 for H.R. was collected. Errors, made in response to word and nonword targets, were classified as follows.

1. Left-sided word neglect errors. These are errors in which the response is a real English word and in which the right side of the target and the response are identical but no common letters appear to the left of a 'neglect point' (following Ellis *et al.*, 1987). An example might be FEATHER → 'heather' where the neglect point falls to the left of the 'e'. This is a stringent criterion since it excludes errors such as 'flashing' for 'fishing' because of the shared 'f'. We have adopted a particularly conservative criterion (as did Ellis *et al.*, 1987), to protect against false positives, since at this stage we do not have a good understanding of the mechanism producing the errors.

TABLE 3. DISTRIBUTION OF ERROR RESPONSES FOR WORD AND NONWORD TARGETS FOR A.H. AND H.R.

Error types	*Percentages* *H.R.* *(n = 128)*	 *A.H.* *(n = 101)*
Neglect errors		
Word responses	63	32
Nonword responses	15	29
Total	78	61
Other errors		
Word responses	9	7
Nonword responses	13	32
Total	22	39
Neglect errors (collapsed across word and nonword responses)		
Substitution	56	40
Addition	10	2
Deletion	12	19
Total	78	61

2. Left-sided nonword neglect errors. These are neglect responses as defined in (1) above but the response is a nonword rather than a word, for example, FEATHER → 'meather'.

3. Other word errors. These are real English words which do not meet the criterion for inclusion in (1) as in the example cited above (FLASHING → 'fishing').

4. Other nonword errors. These are nonwords or neologisms which are visual errors of mixed visual and neglect errors (e.g., OVER → 'iven') in which letters of the target appear on both the left and right of the response.

The neglect errors were analysed further in terms of letter substitutions (letters replaced to the left of the 'neglect point', e.g., TRACE → 'grace'), letter deletions (initial letters of word omitted, e.g., FARM → 'arm') and letter additions (additional letters attached to the left of the target, e.g., AMPLE → 'sample').

The error responses reveal qualitatively different patterns of performance for the 2 subjects (collapsed across all error types $\chi^2 = 11.5$, $P < 0.05$; collapsed across neglect error types $\chi^2 = 7.6$, $P < 0.05$). H.R. produced a preponderance of real word responses (overall 70%), most of which were left-sided neglect errors (63%). He produced relatively few addition and deletion errors while substitution errors made up the majority of his neglect responses. The tendency to lexicalize was less marked in A.H. who produced a relatively high proportion of nonword responses (overall nonword responses 61%) often resulting from a substitution or a deletion response, for example, CAB → 'ab' and RIDE → 'de'. The presence of neologistic nonword errors is unusual in neglect dyslexia and, as we argue later, may have something to do with the severity of the underlying deficit.

Experiment 2: Contribution of lexical knowledge

Having established that both subjects were affected to some extent by the physical dimensions of the stimulus with A.H. being by far the more affected of the two, we then proceeded to examine the effects of higher-order knowledge on reading performance.

Several previous studies have reported that words are less subject to neglect than nonwords (Sieroff *et al.*, 1988; Brunn and Farah, 1990, and E. Sieroff, personal communication, 1989) although there are instances when this does not occur (Ellis *et al.*, 1987). If a distinction between words and nonwords were observed in our subjects, it would be reasonable to conclude that top-down knowledge of lexical identity was exerting an effect on behaviour. Aside from examining the lexical effects of stimuli, we also examined whether certain psycholinguistic dimensions occurring within the class of words also influenced performance. It has been suggested that patients with neglect dyslexia tend not to violate the morphemic structure of words but rather to break words along meaningful boundaries (e.g., CLEVER → 'lever' or 'ever' but not 'ver'; Friedland and Weinstein, 1977), indicating sensitivity to high-level psycholinguistic information. Morphemes are the smallest free-standing units of language that contain unique meaning (e.g., the word 'cow' contains a single morpheme whereas the word 'cowboy' contains 2 morphemes). The following experiments were therefore designed to assess whether the subjects adhered to morphemic boundaries. If this were so, it would indicate that neglect was implicated at a late stage of processing once this high-level morphemic information was recovered.

Lexical status effects

A list of 216 stimuli of 3–7 letters in length of which half were words (e.g., MOUSE) and half nonwords (e.g., POARD) was presented for oral reading. H.R. read 63% of words and 8% of nonwords correctly and A.H. read 42% of words and 3% of nonwords accurately. The proportion of neglect errors (out of total number of errors) as a function of lexical status is shown in fig. 2.

H.R. produced significantly more neglect errors (Fisher's exact test $P = 0.028$) on nonwords than on words, whereas A.H. did not show a difference in performance as a function of lexical status (Fisher's exact test n.s.).

Discussion. The results demonstrate a word superiority effect for both subjects with better preservation of words over nonwords in terms of overall accuracy of report. This effect was more marked for H.R. who also showed a greater tendency to produce neglect errors in response to nonwords rather than to words. It is important to note, in this context, that A.H. also performed better on words than on nonwords but that the type of error response was equally distributed across target type. The implications of this will be discussed later.

Morphemic effects. These experiments contrasted the effects of neglect on reading words that contained a free-standing morpheme on the right (e.g., pea*nut* or f*arm*) from words that did not (e.g., pis*tol* or e*ast*). The sets of stimuli for assessing these effects were as follows. (1) Compound words: a list of 50 compound words and 50 control noncompound words, matched for length, syllable structure and frequency was presented to the subjects. Compound words contained an embedded word on the right (e.g., 'nut' as in pea*nut*) whereas control words did not (e.g., pistol). (2) Embedded words: 216 words and nonwords were

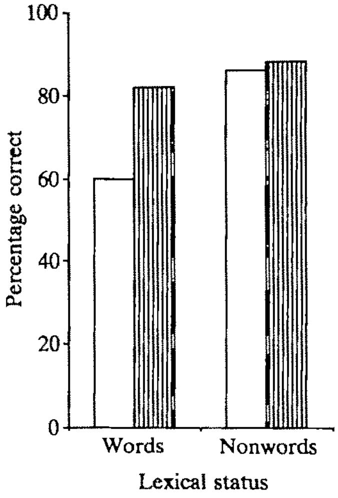

FIG. 2. Proportion of neglect errors as a function of lexical status for A.H. and H.R. Open areas = H.R.; striped areas = A.H.

selected for presentation. Half of the words and nonwords contained morphemes embedded on the right-hand side (e.g., 'arm' as in *farm* and *garm*) whereas the other half did not (e.g., 'ast' as in *east* and *wast*). The length of the embedded morpheme ranged from 3 to 5 letters and the total length of the stimuli ranged from 4 to 8 letters. Overall accuracy on compound/control and embedded/nonembedded is presented in Table 4.

TABLE 4. PERCENTAGE OVERALL ACCURACY FOR H.R. AND A.H. ON EXPERIMENTS EXAMINING HIGHER-ORDER EFFECTS

	H.R.	*A.H.*
Compound words	43	74
Noncompound words	40	68
Embedded words	36	15
Nonembedded words	33	30

Neither subject showed any significant difference in overall accuracy on compound versus control words and on embedded versus nonembedded words (Fisher exact test n.s.). Of greater interest is the relation between error type and the presence of a free-standing morpheme on the right of a stimulus. Table 5 shows the error distribution on the above two lists. Errors classified as 'right-sided word' refer to the reporting of the right-hand morpheme (on compound and word/nonword stimuli) and to the right-hand syllable on control and nonembedded words (e.g., COWBOY → 'BOY' (right-hand morpheme) and PISTOL → 'TOL' (right-hand syllable). 'Other responses' include any other type of error.

TABLE 5. DISTRIBUTION OF ERROR TYPES FOR H.R. AND A.H. ON HIGHER-ORDER EXPERIMENTS (PERCENTAGES)

	H.R.		*A.H.*	
Error types	*Compound*	*Noncompound*	*Compound*	*Noncompound*
Right-sided response	65	7	0	0
Other responses	35	93	100	100
	Embedding	*Nonembedded*	*Embedding*	*Nonembedded*
Right-sided response	36	3	24	30
Other responses	64	97	76	70

H.R. produced more right side errors on the compound and the embedded words than on the noncompound and nonembedded words (Fisher exact test compound/noncompound: $\chi^2 = 34.9$, $P < 0.01$; embedded/nonembedded: $\chi^2 = 16$, $P < 0.01$). There was no significant difference in the number of right-sided responses versus other responses for A.H. on either the compound/noncompound or the embedded/nonembedded list (Fisher exact test compound/noncompound: n.s.; embedded/nonembedded: n.s.).

Discussion. If the right side of a word constituted a free-standing morpheme, H.R. tended to produce the morpheme. If it did not, he tended to report a word of approximately the same length as the target stimulus, neglecting (usually substituting) the left side of the word. This differential distribution of errors depending on whether a right-sided morpheme appears in the stimulus is taken as support for H.R.'s sensitivity to the morphological composition of the word. Although we have shown that A.H. was sensitive to the lexical status of the item, he was not sensitive to the morphemic boundaries of words and this may account for his numerous neologistic responses.

The findings thus far suggest that both subjects were influenced by the lexical status of the target item (more marked in H.R.), indicating that top-down knowledge played a significant role in performance. Even when information appearing on the left was attenuated, higher-level knowledge played a role in reading performance. One well-accepted explanation of the word superiority effect is that existing lexical representations feed down and enhance the perception of the target item; that is, top-down knowledge interacts with low-level processing and helps to overcome the effect of reduced exposure of the stimulus (McClelland and Rumelhart, 1981). The interaction between an early attentional deficit and lexical knowledge is compatible with the present results. In the next experiment, we examined the potency of top-down knowledge in assisting the recovery of low-level information.

Further investigation of morphemic effects

In this experiment, we examined other conditions in which pre-existing lexical knowledge might boost or enhance the uptake of low-level stimulus information. In particular we were interested in knowing whether the pre-existing unified lexical code would be strong enough to provide top-down support for words even when the component morphemes were no longer physically continuous (e.g., COW BOY). A well-documented finding in the neglect literature is that with simultaneous bilateral presentation of two noncontiguous stimuli, subjects neglect the contralesional stimulus even when it appears in the intact visual field, a phenomenon known as extinction. When a single word is presented which subtends the same visual angle as the 2 shorter words, extinction is less likely to occur, indicating that physical contiguity is an important variable in the extinction phenomenon (Sieroff and Michel, 1987). In addition to spatial contiguity, the lexical status of the stimulus has also been shown to be an important contributing factor. Sieroff *et al.* (1988) found that their subject was more likely to neglect the contralesional stimulus when the stimuli were nonwords rather than words, suggesting that top-down lexical influences play a powerful role in reading over and above that played by spatial contiguity.

In the following experiment, we examined whether this interaction between higher-order effects and extinction would also apply to stimuli within the class of words. We selected 100 items made up of 2 morphemes which either formed a compound word (e.g., COW BOY) or did not (noncompound, e.g., SUN TAX) and examined the contribution of spatial contiguity and morphemic relatedness to reading performance. All stimuli were presented for oral reading in H.R.'s intact visual field in the following conditions. (1) Contiguous: the compound and noncompound pairs of morphemes were presented with the morphemes physically adjacent to each other and immediately to the right of a fixation point (*) (e.g., COWBOY and SUNTAX). (2) Non contiguous: the 2 morphemes appeared immediately to the right of a central fixation point but were separated by a single space (e.g., SUN TAX and COW BOY). (3) Contiguous joint presentation: the 2 morphemes were physically adjacent but were separated by a number sign, e.g., SUN # TAX and COW # BOY.

We anticipated that H.R. would report both members of the pair more often when the stimuli were contiguous (as in Sieroff *et al.*, 1988) than when they were noncontiguous and that performance on the contiguous joint condition would fall somewhere between the two. Further, since H.R. was shown to be sensitive to morphemic factors on a previous experiment, we predicted that he would also be affected by the identity of the stimuli. We thus expected performance on the compound stimuli to be better than that on the noncompound pairs, irrespective of physical contiguity. Finally, we predicted that if higher-order information were sufficiently strong, both members of the compound pair would be reported when noncontiguous although not as often as when they were contiguous. The results, shown in Table 6, reflect the percentage of words in which H.R. reported both morphemes of the stimulus, i.e., where no extinction occurred.

There was a statistically significant effect of condition ($\chi^2 = 12.2$, $P < 0.05$) with both morphemes reported most often on the spatially contiguous condition, followed by the joint and then the noncontiguous condition. In addition to the effect of spatial contiguity, a statistically reliable effect of stimulus type was observed with both morphemes of the compound word being reported more often than those of the noncompound words (collapsed across all three conditions, $\chi^2 = 18.1$, $P < 0.05$). This suggests that the

TABLE 6. PERCENTAGES OF BOTH MORPHEMES REPORTED BY H.R. ON THE MORPHEMIC EXTINCTION EXPERIMENT

	Conditions		
Stimuli	*Physically contiguous (e.g., COWBOY)*	*Noncontiguous (e.g., COW BOY)*	*Joint contiguous (e.g., COW#BOY)*
Compound	59	28	48
Noncompound	14	12	9

top-down support of an existing lexical representation increases the probability that H.R. reported the left-sided morpheme. Within the noncompound words, there was no significant difference of mode of presentation (χ^2 n.s.), with the left side being frequently extinguished in all conditions. On compound words, however, there was an effect of mode of presentation with performance on the contiguous condition and joint contiguous condition being equivalent (χ^2 n.s.) but being significantly different from the noncontiguous condition (collapsed across joint and contiguous; $\chi^2 = 12.9$, $P < 0.01$).

Discussion. These results confirm the prediction that the unified lexical code which underlies the paired morphemes of compound words helps to resist extinction of the left-sided stimulus. These findings also provide further support for the contribution of stored lexical knowledge to H.R.'s reading performance. The interaction between distribution of attention and lexical status of the stimulus was also observed in a study of normal subjects by Sieroff and Posner (1988) who modulated the effects of attention by using a digit which appeared prior to the stimulus and cued subjects either to the beginning or the end of the target. Noncompound words (e.g., YARDBACK) benefited from the attentional cueing as did nonwords, whereas compound words (e.g., BACKYARD) did not. These results, like ours, suggest that compound words are processed differently from noncompound words.

In all the above experiments, we have shown that our 2 neglect dyslexic subjects, A.H. and H.R., demonstrated significantly different patterns of performance. One possible explanation for the discrepancy in their behaviour is that there existed a fundamental difference in the nature and severity of the attentional deficit, thereby giving rise to different patterns of reading performance. It may be, for example, that A.H.'s attentional disorder is so severe that he can only pick up some information on the left-hand side (producing a word superiority effect) but that this information is insufficient to activate all forms of top-down knowledge. To substantiate this claim, we attempted to establish how much information A.H. and H.R. were able to process from the left of the stimulus.

Experiment 3: Spatial attention testing

Current theories of attention (Treisman and Gelade, 1980; Posner, 1988; Treisman and Gormican, 1988) distinguish between two modes of processing. One mode involves the detection of the presence of a simple feature among disparate features; for example, when one object differs in orientation from the background, the item 'pops out' of the visual display. Detection of the 'oddball' feature is conducted automatically and in parallel and, according to some views, does not require attention although attention is engaged after the information is processed (Posner and Presti, 1987; Treisman and Gormican, 1988). Attention is mandatory, however, for the second mode of processing when two or more features must be conjoined to distinguish the object from the background, for example, when colour and form are both needed to locate the disparate object or when letter position and identity must be conjoined as in reading. The theoretical distinction between the two modes of processing is derived from experimental work with normal subjects and it is not clear how this might operate in the case of attentional deficits. It may be that even if the simple feature detection is attention-free, the pick-up of low-level features may be impeded if the deficit is severe enough. Employing a similar distinction, Riddoch and Humphreys (1987) showed how simple feature detection was relatively intact with 3 subjects suffering from unilateral neglect but that serial or conjoined processing was impaired.

We predicted that both subjects would show better performance on the left of the display compared with the right, irrespective of the task. Like Riddoch and Humphreys (1987), we predicted that performance on the simple feature task would be better than on the conjoined task for both subjects but that A.H. might be more affected than H.R. on the latter task. In other words, even though both subjects have a deficit in attention, the locus and degree of interference may differ. The tasks were as follows.

Simple feature detection task

A total of 120 horizontal strings of 6 letters appeared on the screen after the appearance of a central fixation point and a 500 ms delay. On half the trials the letters were all alike (e.g., *AAAAAA) and on the other half, a different letter appeared in the array with its position systematically varied across trials (e.g., *ACAAAA). The subjects were required to judge whether all the letters were the same or not. Accuracy of 'oddball' detection by character position was calculated.

Conjunction of features

A total of 120 horizontal strings of 6 different upper case letters appeared on the screen for oral report after the central fixation point and 500 ms delay (e.g., MXRTBG). Accuracy of report by letter position was calculated. As on previous tasks, A.H. performed both tasks at unlimited exposure duration whereas H.R. received the stimuli at 500 ms exposure duration.

A 3-way ANOVA was conducted with tasks (simple and conjoined) and positions (using all serial positions as individual points) as within-subject variables and subjects (A.H. and H.R.) as the between variable (*see* fig. 3). There was a significant main effect of task (F(1,16) = 5.04, $P < 0.04$), supporting the finding by Riddoch and Humphreys (1987), and of position (F(1,16) = 8.03, $P < 0.02$) as we had predicted. The main effect of subject was not significant (F(1,16) = 2.4, $P < 0.15$) but there was a significant interaction between subject and task (F(1,16) = 7.18, $P < 0.04$) as evident from the superior performance displayed by A.H. on the conjoined task in positions 4–6 relative to H.R.

Discussion. H.R.'s overall performance on the simple task was superior to that on the conjoined task, with the left side being impaired relative to the right equally on both tasks. Information was being picked

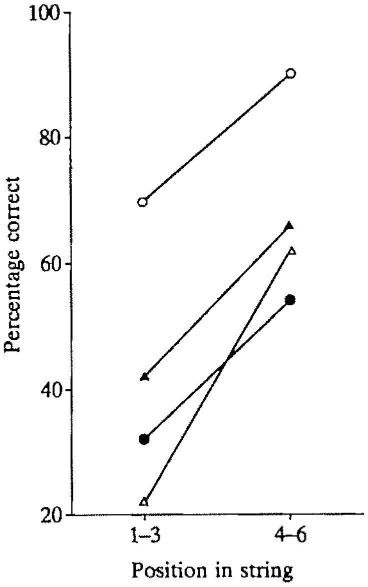

FIG. 3. Percentage correct letter report as a function of position of target on simple and conjoined feature detection task. Open circle = H.R., simple; filled circle = conjoined; filled triangle = A.H., simple; open triangle = conjoined.

to an equal degree in both tasks but when attention was required to conjoin the information, the task became more difficult.

A.H.'s difficulty in the simple feature detection task for material on the left-side of space, already more pronounced than H.R.'s was exaggerated on the conjoined task. In the right-most positions, A.H. was able to perform the simple and conjoined tasks equally well. This implies that basic feature information was not being picked up well on the left-hand side of the array and when that information was used for conjunction of features, the deficit became even more apparent. This inability to encode information on the left was not the result of a primary sensory loss (visual field defect) but was attributable to a fundamental attentional deficit, as will be demonstrated later in Experiment 5.

These data are compatible with the suggestion that A.H. cannot make use of top-down knowledge since he cannot assemble a reasonable representation of the visual stimulus. H.R. is able to take advantage of stored lexical knowledge which is then used to assist in the interpretation of the stimulus.

The serial position curves for both subjects (*see* fig. 3) support the view that information appearing on the right is processed better than information on the left. This is consistent with the view that attention is distributed as a gradient across the field with the lowest level of activation on the left (Kinsbourne, 1987; De Renzi *et al.*, 1989). If this hypothesis is indeed correct and performance is simply a function of where the stimulus appears along the gradient of attention, then moving the stimulus into a more optimal attentional region should result in improved performance for both subjects. The next experiment corroborated this prediction.

Experiment 4: Location effect

A list of 60 words of 3–5 letters (mean frequency 239 per million; Francis and Kučera, 1982) and 20 nonword foils was presented in two different locations, starting either immediately next to fixation (near condition; visual angle 2.3°–3.4°) or starting at the fourth character position to the right of the fixation point (far condition; visual angle 4.6°–5.7°). Care was taken to ensure that the stimuli were still within the range of good visual acuity. We predicted that performance should be superior in the far condition, i.e., when stimuli fell in a more optimal region of attention.

The results revealed significantly better performance for both subjects in the far condition as compared with the near presentation. H.R. reported 17/60 words correctly when they appeared next to fixation and 27/60 words correctly when they were further over into right hemispace (McNemar's test $\chi^2 = 4.5$, $P < 0.05$). A.H.'s behaviour followed a similar trend, although the effect of location was not as strong. He reported 24/60 words correctly next to fixation and 32/60 correctly in the more displaced location (McNemar's test $\chi^2 = 3.6$, $P < 0.10$).

Discussion. Both subjects showed superior performance when the stimuli appeared further over into right hemispace, lending support to the hypothesis of a gradient of attention. These results are also consistent with the general finding in the neglect literature that the severity of neglect decreases as one moves even a small distance further into ipsilesional hemispace (Heilman and Valenstein, 1979; Butter *et al.*, 1988). The general explanation for this finding is that the amount of neglect is decreased when the stimuli are presented in an area of optimal attention, i.e., further to the right along the gradient.

The gradient explanation has been used previously to account for neglect dyslexia (Kinsbourne and Warrington, 1962) and our data provide empirical evidence which corroborates this attentional hypothesis. Our finding suggests that the fundamental deficit is clearly one of visual spatial attention but depending on the location of the stimulus along the attentional gradient, more or less information may be neglected during reading.

Experiment 5: Manipulation of attention

In view of the fact that A.H. picked up so little information on the left-hand side, it may be tempting to ascribe his neglect of the left side to a primary sensory or perceptual deficit. If this were indeed the case, the above results would have no bearing on the issue of selective attention. To exclude this possibility, we designed a task to demonstrate that A.H. can be cued to attend to the left. We expected that when his gradient of attention is shifted so that stimuli appear in a more optimal region, he would be able to report more information appearing on his previously neglected side. This would effectively exclude a primary sensory deficit as an explanation for his impaired performance. In addition, we expected that if our interpretation is correct, then A.H. like H.R., would then show sensitivity to morphemic boundaries. In other words, when attention is operating more efficiently, the low-level information would be picked up and the opportunity for top-down support and lexical enhancement would be provided.

Fifty trials of 2 morphemes separated by a single character space were presented to A.H. for unlimited viewing time to the right of a central fixation point. In half of the trials, the 2 morphemes formed a compound word (e.g., *COW BOY) whereas in the other half the 2 morphemes were unrelated (e.g., *SUN TAX). The trials were presented in two conditions. (1) Baseline condition: A.H. was instructed merely to read the 2 words on the screen. (2) Attentional manipulation: A.H. was instructed to report the left-sided word first followed by the right-sided word. Karnath (1988), in a similar task using nonverbal material, showed that reducing information analysis on the right side by instructing subjects to attend to the left, provoked a covert shift of attention to the left side. A.H. was instructed to maintain central fixation throughout.

In the baseline condition A.H. reported both words correctly in only 2 out of 50 trials whereas he reported both words correctly on 28 trials when attention was manipulated. Of these 28 trials, 21 were from the list of compound words whereas the remaining 7 were unrelated morpheme trials.

Discussion. The improvement observed on the manipulation task suggests that A.H. is able to pick up information from the contralesional side if he consciously directs his attention to the left. His neglect dyslexia, therefore, cannot be attributed to a primary visual problem which precludes processing of left-sided information. While his attention may be automatically directed to the right, he can voluntarily shift it to detect information on the left. No obvious shifts in eye movements accompanied his performance and the orientation to the left may therefore be attributed to a covert attentional shift. The fact that A.H. was able to attend to material appearing on the left, when cued to shift his attention consciously in that direction, supports the claim that attention may be voluntarily directed to the neglected side either by a cue (Riddoch and Humphreys, 1983) or by task instructions (Karnath, 1988). Furthermore, the increased probability of reporting both morphemes when they form a compound word suggests that lexical knowledge plays a critical role in performance. Thus when the stimuli appear in a region where the attentional gradient is sufficiently high to allow a critical amount of information to be processed, an interaction with stimulus type emerges. Even when the information on the left was somewhat attenuated, higher-level morphemic knowledge therefore assisted in recovering information when the 2 morphemes formed a compound word but not when they were unrelated. As for H.R., then, A.H. did demonstrate an interaction between a low-level attentional deficit and higher-order knowledge provided that sufficient information was picked up from the left to activate the top-down knowledge.

GENERAL DISCUSSION

The goal of this paper was to document the locus of breakdown of attention in visual processing of verbal material and to describe the effect of the attentional deficit on the reading performance of 2 subjects with neglect dyslexia. Both subjects possessed intact central representations of words as evidenced by their ability to spell orally and to write correctly. Their left-sided neglect only became manifest on reading single words and text. The modality-specific nature of the impairment is consistent with the view that attention is disrupted peripherally rather than in a central mechanism or 'conceptual space' (Barbut and Gazzaniga, 1987) which is common to all modalities.

Although both subjects exhibited some disruption of visual attentional processing, a more detailed examination of their performance revealed what appears to be a double dissociation. On the one hand, A.H. was susceptible to structural manipulations (such as length and horizontal extent) which altered the low-level representation of the word. This indicates that the attentional disruption is data-driven and stimulus-bound, supporting the view that attentional selectivity takes place early in the system. H.R. did not demonstrate these low-level effects. Instead, he was influenced by the lexical and morphemic status of the stimuli, thereby supporting the hypothesis that attentional selectivity takes place late in the system once the stimuli have been identified and their psycholinguistic features have been accessed.

This apparent double dissociation of physical low-level versus lexical higher-order effects may be taken as evidence for separate patterns of breakdown, one affecting early processing and the other affecting later processing. This account fragments the neglect dyslexia syndrome and posits two separate loci of breakdown. While this fragmentation account captures some of the data, it cannot account for all of the findings. For example, in addition to high-level factors, H.R. also showed some sensitivity to the physical parameters of the stimulus as his performance was influenced by the orientation and location of the item in the visual field. Furthermore, A.H. was not affected only by low-level stimulus dimensions but also by the lexical status of the items as evident by his word superiority effect. The paradox thus becomes apparent—a clear separation into perceptual versus conceptual effects does not suffice and an alternative explanation is required.

We offer one possible explanation for these apparently contradictory findings. Our explanation depends on the assumption that the symptoms shared by the subjects differ in degree. In proposing a unitary framework, we have taken the evidence from both subjects in tandem. While the effects of conceptual factors and low-level manipulations were most noticeable in H.R. and A.H., respectively, we assume that both types of effects were operating in both subjects but that the overt symptoms of one or the other were obscured or masked, depending on the extent of the attentional deficit.

Attention which is disrupted early does not affect information processing in an all-or-none fashion but is unevenly distributed as a gradient from left-to-right. Features appearing on the left are picked up poorly but may often be sufficient to activate top-down knowledge. This higher-order knowledge is brought to bear on the encoded information, enhancing and improving performance and giving rise to higher-order effects. This interaction between an early deficit and existing knowledge was less obvious for A.H. whose attentional gradient was very steep. Thus information on the left was so poorly registered that it could not trigger the existing lexical and morphemic representations. When the information was shifted into a more optimal region of the attentional gradient (Experiment 4), top-down effects became apparent. H.R.'s attentional gradient was less severe, allowing higher-order effects to be readily observable. In the context of a unitary explanation, the critical distinction between our subjects, then, is in the severity of the attentional disturbance or the slope of the attentional gradient (Experiment 3). A.H. and H.R. are thus parametric variations of the same basic attentional disruption which appears at an early processing stage. Depending upon its severity, the attentional deficit may or may not give rise to interactions with later processing stages. Any simple explanation of peripheral versus central or early versus late attention, therefore, cannot suffice.

A model to explain both subjects' deficits could operate as follows. H.R.'s primary attentional deficit results in decreased attention to the left-hand side but information from the left, although much attenuated, is still processed. A 'clean-up' operation, which has access to the stored representations of words, then takes the perceptual data and constructs the most consistent and plausible interpretation of the incoming information. Thus words are read better than nonwords, right-sided morphemes are reported when possible, and compound words are preserved relative to two unrelated morphemes. A.H.'s primary attentional deficit is more severe, affecting even the detection of fundamental features. Since the clarity of the perceptual data is diminished, the 'clean-up' operation may be compromised so that he cannot benefit much from interactions with higher-order knowledge.

A model with these essential features and functions has been developed by Mozer (1987, 1988). This connectionist model, MORSEL (multiple object recognition and attentional selection), is a parallel distributed processing model capable of recognizing multiple words appearing simultaneously on its 'retina'. The network consists of a letter and word recognition modules through which activations from the 'retina' are propagated. MORSEL also has a module in which higher-order lexical and semantic information is stored. Critical to our account is the fact that MORSEL has an attentional mechanism that controls the amount and sequential order of information flowing through the system. An 'attentional spotlight' is constructed across some region of the 'retina' facilitating preferential processing of sensory information from that area.

If attention is distributed as a gradient from left-to-right (as in neglect), the rightmost information will always have an advantage over the left-sided information. Information on the left will also be processed but in a more probabilistic fashion. If this left-sided 'unattended' information is sufficiently activated, it may engage higher-order knowledge which feeds down and assists in the recovery of the attenuated left-hand side. Such a 'clean-up' mechanism may not be possible if insufficient left-sided knowledge is propagated forwards, that is, if the gradient is too severe. MORSEL is an implemented, working computational model and, in the past, has been able to account for a broad range of empirical psychological phenomena. Using a 'lesioned' version of MORSEL in which the attentional mechanism has been selectively 'lesioned' (Mozer and Behrmann, 1990), we have successfully simulated the behaviours of A.H. and H.R. The results of these simulations suggest that manipulations of the severity of the attentional gradient can account for the differences in performance between subjects.

The findings from both the clinical and the simulation studies indicate that neglect dyslexia is a heterogeneous phenomenon. Our assertion, however, is that the heterogeneity arises not from different loci of breakdown but from the severity of the attentional disorder. In one case, the disorder leads to what appears to be a low-level deficit and in the other, to a more complex pattern that is receptive to higher-order lexical influence. In this formulation, both manifestations of the disorder arise from a single cause, an uneven distribution of attention within the retinal frame.

It is possible, therefore, that a unitary explanation can account for and resolve the individual differences and discrepancies that exist in the literature. The patient of Ellis *et al.* (1987) demonstrates effects which are similar to those of A.H. in that the disorder occurs early in the reading process. Sieroff *et al.* (1987), on the other hand, describe top-down effects which are more in keeping with H.R.'s pattern than A.H.'s disorder. We suggest then that a detailed analysis of neglect dyslexia in all subjects may highlight the commonalities rather than the differences. The differential results shown by A.H. and H.R. have bearing on the role of spatial attention in normal visual processing. Disruption of attention at an early stage need not affect processing in an all-or-none fashion. The pick-up of low-level information may be impeded but the information that does get through can be combined with knowledge of stored representations so that perceptual information may be accurately recovered. The dichotomy of early and late selection and of pre- and postidentification procedures may be an over-simplification of the way in which attention functions in visual processing. We suggest that a 'hybrid' view may be a closer approximation to reality (Pashler and Badgio, 1987; Mozer, 1988).

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PROCESSING OF LOCAL AND GLOBAL MUSICAL INFORMATION BY UNILATERAL BRAIN-DAMAGED PATIENTS

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SUMMARY

Melody processing in unilaterally brain-damaged patients was investigated by manipulating the availability of contour and metre for discrimination in melodies varying, respectively, on the pitch dimension and the temporal dimension. On the pitch dimension, right brain-damaged patients, in contrast to left brain-damaged patients and normal controls, were found to be little affected by the availability of contour as a discrimination cue. However, both brain-damaged groups were impaired on tasks requiring consideration of pitch interval structure. These findings are consistent with hierarchical contribution of the cerebral hemispheres, with the right hemisphere being primary in representing the melody in terms of its global contour and the left hemisphere by filling in the intervallic structure. On the temporal dimension, only the discrimination of durational values (the rhythm) was found to be impaired by a lesion in either hemisphere, which spared, however, the metric interpretation of the musical sequences. These latter results are discussed in the light of current models of temporal processing. Finally, evidence of double dissociation between the processing of the pitch dimension and the processing of rhythm was obtained, providing further support for the need to fractionate musical perceptual abilities in order to arrive at a theory as to how the two hemispheres cohere to produce a musical interpretation of the auditory input.

INTRODUCTION

Establishing hemisphere dominance for music has long been the main objective of the study of amusias, that is, the study of the impairment of musical abilities from acquired diseases of the brain. Such persistence in searching for the basis of music processing in terms of hemisphere dominance is understandable when considering its history. For almost a century, all case reports described patients who became amusic after damage to their left (speech dominant) hemisphere (*see* Henschen, 1926, and Dorgeuille, 1966, for surveys). At the turn of this century, when rejection of the single case approach motivated the assessment of series of patients, music processing was attributed to the right hemisphere (*see* Zatorre, 1984, and Peretz, 1985, for reviews). This conflicting set of data later found a plausible explanation in the results obtained by Bever and Chiarello (1974). These authors showed that the hemisphere lateralization for melody processing was dependent on the musical expertise of the subjects. Musicians were found to process melodies predominantly in the left hemisphere (as indicated by a right ear

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advantage) whereas nonmusicians did so predominantly in the right hemisphere (as indicated by a left ear advantage). This finding is consistent both with the data showing a left hemisphere predominance, since case reports are typically restricted to proficient musicians, and the data indicating right hemisphere superiority, for in group studies subjects are usually not selected with respect to musical training, which would then be modest.

The Bever and Chiarello study was influential not only because it had explanatory value but also because it led to the development of new conceptions relating to the nature of hemisphere differences for music processing. The idea put forward in that study was that the functioning of each cerebral hemisphere is characterized by a different mode of processing. The left hemisphere would be better equipped to deal with local information in melodies, while the right would be superior for dealing with global information. Although this distinction has been criticized, especially when applied across cognitive domains (*see* open peer commentaries to Bradshaw and Nettleton, 1981, and Bertelson, 1982), it has generated successful predictions regarding lateralization in normal subjects. Such a favourable outcome can probably be attributed to the fact that in music, contrary to other cognitive domains such as vision, the specification of local and global features are unambiguously provided by independent theories.

Over the last decade, the information-processing approach to music perception has been devoted mainly to the definition of the types of features in a melody that are selectively encoded in order to allow for discrimination and recognition. Two types of features or properties have been identified as functionally important in the processing of sequential pitch patterns: the pitch of individual tones or the interval size between two adjacent tones, and the contour, which characterizes pitch directions independently of the precise pitch values (*see* Pick, 1979, and Dowling, 1982, for reviews). The use of these two types of features, that have been classified as local and global (Laberge, 1981; Dowling, 1982), respectively, depends mainly on the experimental conditions. In particular, the importance of the global contour relative to the local intervals depends, for both musicians and nonmusicians, on factors such as time constraints, novelty of the material and application of transposition. It appears that the most immediate form in which melodies are encoded and/or retrieved from memory when first heard is in terms of its contour. The encoding of specific intervals or individual pitches seems to take time, and thus mainly assists delayed recognition of novel melodies (Dowling and Bartlett, 1981; Dewitt and Crowder, 1986) and recognition of familiar melodies (Dowling and Fujitani, 1971). The importance of the contour cue is even more apparent when melodies must be recognized after transposition, probably because the establishment of a new key, and hence the anchorage of local information, requires accumulation of local evidence (Edworthy, 1985).

The work done in the field of cognitive psychology thus allows more precise definitions, not only of what are the local and global features that are extracted in melodies, but also of the appropriate conditions promoting their use. These propositions can therefore serve as guidelines for studying hemisphere differences. Indeed, the data that we have collected so far with normal subjects along these lines are quite encouraging (*see* Peretz and Morais, 1988, for a more extensive review). To illustrate the close correspondence between this distinction emanating from an information-processing approach to melody perception and the division of functions between the cerebral hemispheres, we will briefly describe two previous results that are most relevant to the present study.

One piece of evidence in favour of local pitches and global contour representations having a differential hemisphere dominance was provided in a study where subjects were required to classify successive melodies as 'same' or 'different' (Peretz and Morais, 1987). The contour of the melodies to be differentiated was manipulated so that it was violated, and thus available for discrimination, on half the trials and was preserved on the other half. A clear facilitative effect of contour was observed, contour-violated melodies being far better discriminated than contour-preserved melodies. Moreover, a left ear advantage (LEA) was obtained in the first case and a right ear advantage (REA) in the second. It can therefore be inferred that the subjects tended to rely on contour representation to discriminate the melodies, and that this representation mainly involved the right hemisphere. When this global cue was not available for discrimination, such as with contour-preserved melodies, and subjects must have relied on more local cues, the left hemisphere appeared predominant. Another way to manipulate the melody properties in order to further restrict the manner in which melodies are processed is to exploit melody transposition. It has been repeatedly observed that melody comparison after transposition (i.e., through a change in pitch level) hinders access to intervallic structure and promotes the use of contour for discrimination (Dowling, 1978; Edworthy, 1985). Thus application of transposition should promote the contribution of the right hemisphere. The finding of an increased LEA in such conditions corroborates this assumption (Peretz, 1987).

It should be pointed out, however, that all these manipulations of melody properties were examined with laterality paradigms in normal subjects. We still know very little indeed about how brain damage interferes with these different aspects of melodies. The only study that has so far tackled this issue (Zatorre, 1985), led to inconclusive results. All patients, irrespective of the side of the unilateral temporal lobectomy, displayed similar sensitivity to contour and interval cues. One likely explanation is that contour and interval processing are mediated by neural circuitries that extend beyond temporal regions. However, as isolated negative results can be due to a variety of uncontrolled factors, it seemed worthwhile to study this issue further in brain-damaged populations. This was the major goal of the present study.

Therefore, in line with our earlier work done with normals, patients with brain damage restricted to one cerebral hemisphere were presented with contour-violated, contour-preserved, and transposed melodies in three different conditions, all requiring a 'same-different' classification task. It was predicted that patients with left hemisphere damage (LHD) would exhibit greater sensitivity to contour manipulation than patients with right hemisphere damage (RHD). However, LHD would be as impaired as RHD, compared with normal controls (NC), on conditions requiring pitch interval consideration. This latter hypothesis emanates from the idea that contour representation might be necessary for embedding interval information (Peretz, 1985). If this notion is correct, the detrimental effect that is expected from a right hemisphere lesion on the contour description of the pitch pattern should also deprive subjects of the necessary anchorage points for pitch interval encoding. In addition, since local pitch information is essential for delayed recognition of novel material (Dowling and Bartlett, 1981; Dewitt and Crowder, 1986), it was predicted that both RHD and LHD would exhibit poor delayed recognition of the material presented in comparison to NC. To assess this further prediction, a delayed recognition task was presented to the subjects at the end of the testing session.

Finally, since a group study of this type is very lengthy (it took 4 yrs to complete this one) due to the restrictive criteria used here for patient selection (*see* subject description), it was deemed worthwhile to explore similar ideas in the temporal domain. As this area is largely neglected in the field of neuropsychology, at least within an information-processing approach, the extension of this study to the processing of the temporal information was considered exploratory. Nevertheless, there are grounds for assuming that the processing of temporal structure in a melody is (1) not clearly lateralized to one cerebral hemisphere (Peretz and Morais, 1980, 1988) and (2) probably subserved by more than one mechanism. With regard to the latter hypothesis, which is of major concern in the present context, it has been argued that listeners use metric beat patterns as a framework within which to judge and produce precise rhythmic values (Povel, 1984; Shaffer *et al.*, 1985; Dowling and Harwood, 1986). Indeed, it is widely held that under the commonsensical notion of 'rhythm', two different types of temporal organization coexist: the metre, which refers to the perceived beat marking off equal durational units and the arrangement of these beats into bars (or measures) that place a major accent on the first beat (and which allows one to distinguish a waltz from a march); and the rhythm, which refers to the organization of relative durations of tones and silent intervals without regard to periodicity. In this context, it is speculative, yet reasonable, to draw an analogy between the processing of contour and interval sizes in sequential pitch patterns and the processing of metre and durational values (rhythm) in sequential temporal patterns. Assuming that meter characterizes global temporal organization of a melody, as does contour on the pitch dimension, a right hemisphere predominance is expected. Alternatively, if durational values are to the temporal dimension what pitch intervals are to the pitch dimension, a left hemisphere superiority is expected for processing rhythmic organization.

In order to assess this hypothesis, with respect to the temporal organization of sequential patterns, we designed two tasks: a standard 'same-different' classification task and a new 'waltz-march' classification task. In respect to the former, nonmusicians were induced to rely on rhythmic organization, for this was the only cue available for discrimination. This condition will be referred to as the rhythmic task. In contrast, in the other condition, a 'waltz-march' classification task was used in order to promote metrical organization of the sequences. Such a judgement might be closer to what listeners do implicitly when hearing the first bars of a musical piece in order to get ready for dancing.

In summary, the aim of the present study was to address essentially two questions.

Given that music perception can be affected by a unilateral vascular lesion (Benton, 1977), (1) what can these impairments tell us about the contribution of each hemisphere to music processing? and (2) what can these deficits tell us about existing models of normal music processing? The main hypothesis is that the local versus global nature of the features to be abstracted in melodies is a major determinant of the functional differences between the hemispheres. Accordingly, a lesion in the right hemisphere is expected to produce a double deficit, in the building of contour and metre representations and in the anchorage of local information, such as pitch intervals and durational values. In contrast, a lesion in the left hemisphere is expected to interfere with the processes involved in the extraction of local features but to spare the ones involved in global processing, in comparison with the performance of NC. In addition to these general functional dissociations predicted at the level of the groups, it was hoped that evidence of double dissociation between temporal organization and pitch organization might be discovered at the level of single cases. Indeed, there are both theoretical and empirical reasons to expect the pitch structure and the temporal structure of musical sequences to be processed by autonomous subsystems (Peretz and Morais, 1989).

METHODS

Subjects

Twenty unilateral brain-damaged patients and 20 normal controls (NC) volunteered to serve as subjects. Informed consent was obtained from all of them. All brain-damaged patients had suffered from a first unilateral cerebrovascular lesion. The nature of the damage for all subjects was verified by CT scan examination. Our criterion for brain damage location was that unilateral damage had to be unequivocal across neurological and neuropsychological measures. Moreover, audiometry had to be in the normal range for the patient to be included in the present study. A history of alcohol abuse, psychiatric disorder or other neurological illness was grounds for exclusion. Finally, about half of the LHD had to be discarded because of language difficulties that would have interfered with the comprehension of the instructions. Thus, 8 of the 10 LHD had some aphasic problems but in a mild form, 7 of the 10 RHD had mild hemispatial neglect. All patients suffered motor difficulties on the contralateral side and were tested no sooner than 3 wks postlesion. They were inpatients either at the Hôpital Universitaire Brugman (Brussels) or at the Hôpital Côte-des-Neiges (Montreal).

The NC were hospital staff or volunteers from senior citizen's centres; each control was selected so that he/she matched as closely as possible in age, sex, education, musical background and occupation with one of the brain-damaged patients. The mean age (yrs) of each group was as follows: LHD 62 (range: 49–72); RHD 58 (range 35–79); NC 61 (range 38–77). The mean number of yrs of education were: LHD 10 (range: 9–13); RHD 12 (9–17); NC 11 (9–17). The analyses of variance confirmed that none of the subject groups differed significantly in age ($F(2,37) = 0.01$) and in number of years of education ($F(2,37) = 0.37$).

All subjects were right-handed as assessed by a handedness questionnaire (Oldfield, 1969). No musician, either amateur or professional, participated in this study. Only 10% of the subjects in each group could be considered as having some musical experience, that is between 2 and 5 yrs of formal musical training. In addition, only relatively educated subjects (with a minimum of 9 yrs of academic education) were tested. This selection criterion was set up after having observed that many normal subjects with about 6 yrs of education failed to discriminate contour-preserved melodies above chance (Duchatelet, 1986).

Material and apparatus

A set of 6 subtests, described hereafter by the major musical dimension manipulated, were constructed from the same pool of 24 novel musical sequences. These sequences were tonally structured and made up of two phrases following Schoenberg's (1942) principles. Half were written in a duple metre, half in a triple metre. These two-phrase sequences were used in the metric condition; for all the other conditions, only the second phrase of each sequence served as stimuli. These second phrases were 4 bars long, lasted about 4 s, and contained from 8 to 19 tones (mean=10.7). The choice of the second phrase, instead of the whole sequence in all conditions but the metric task, was motivated by the need to reduce the length of the testing session as much as possible. Moreover, since with these isolated phrases normal subjects were already performing close to ceiling, use of the shortest version was highly desirable. This was not the case for the metric task. Pilot work (Delier, 1985) indicated that normal subjects needed to accumulate substantial evidence before making a reliable metric decision. Therefore, for this particular test, presentation of the two-phrase sequences was required.

All stimuli were played on a recently tuned piano and recorded on a Revox A 77 tape recorder. During the experimental sessions, the prerecorded tapes were also played on this apparatus.

Pitch organization conditions. Three types of manipulation were applied to the second phrase of the 24 initial sequences. One manipulation consisted of transposing each sequence to a near key, either by raising each pitch by a perfect fifth (*see* B in fig. 1) or by diminishing each pitch by a fourth. These distances were the ones used in prior work with normals (Peretz, 1987). Another manipulation consisted of creating a contour-violated alternate melody by modifying the pitch of one tone so that it changed the pitch direction of the surrounding intervals (*see* C in fig. 1, for an example of these contour changes. i.e., the interval directions surrounding the critical pitch have been modified from −, + to 0, −), while keeping in the original key. The serial position of this modified pitch varied across melodies. The third manipulation consisted of creating a contour-preserved alternate melody of these contour-violated melodies by modifying the same critical pitch to the same extent (in terms of semitone distance), but in keeping with the original contour and scale (*see* D in fig. 1).

Three sets, each consisting of 2 practice trials and 24 experimental trials, were constructed with these

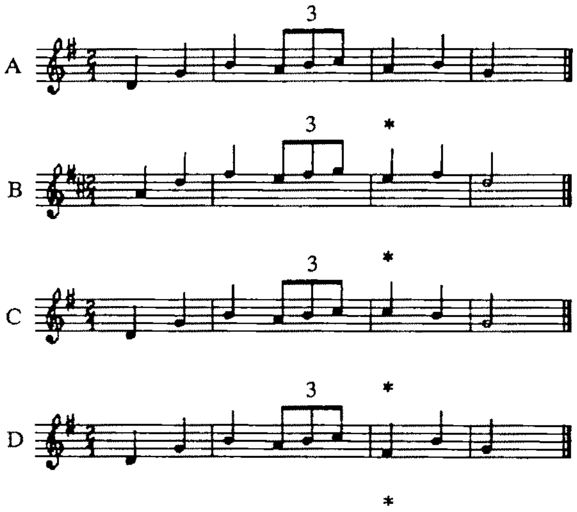

FIG. 1. Example of an initial melody (A), its transposition (B), its contour-violated (C) and its contour-preserved transformation (D). *Modified pitch.

melodies. Each trial consisted of a warning signal and a target melody followed, after a 2 s silent interval, by a comparison melody. Duration of the intertrial interval was 5 s long. A first set, prepared for the contour-violated condition, was constructed so that 8 trials were made of identical melodies (i.e., 2 different renditions of the same target melody) and 16 trials of different melodies, consisting of the contour-violated pairs (e.g., A and C in fig. 1). The second set, prepared for the contour-preserved condition, was similar to the contour-violated condition set in keeping the same target melodies; the only modification was that each different comparison melody was replaced by its preserved-contour alternate (e.g., A and D in fig. 1). The third set was created by copying first, in a random order, half of the trials of the contour-violated set and half of the trials of the contour-preserved set. Each target melody of this latter set was then replaced by its transposed version (e.g., A by B in fig. 1). Therefore, on each trial of this latter set prepared for the transposed condition, the target melody was always higher or lower in pitch level than the comparison melody, which remained, however, identical across the three sets.

Note that, in each set, there were twice as many 'different' as there were 'same' trials. Such construction was motivated by the need to reduce the length of the testing session, while preserving all information critical to the present study. Indeed, performance comparison for the 'different' trials through contour and transposition manipulation was the only way to infer the nature of the melodic cues abstracted by the subjects.

Temporal organization tasks. As specified earlier, the 24 entire two-phrase sequences served here as stimuli for the metric task. Each sequence (*see*, e.g., A in fig. 2) was recorded here in a random order with an intertrial interval of 5 s. These experimental trials were preceded by 4 practice trials made up of similar but different sequences.

For the rhythmic task, the stimuli were derived from the second phrase of the 24 sequences used in the metric task, in order to correspond to the temporal structure of the target melodies used in the pitch organization conditions. Two manipulations were applied to these isolated phrases. One manipulation consisted of removing all pitch variations by tapping the temporal patterns, in keeping the original beat structure; care was taken as to mark the metre by placing an intensity accent on the first beat of each measure (*see* B in fig. 2, that represents the tapped version of the second phrase of A). These patterns served as targets. The second manipulation, applied to create different comparison patterns, consisted of modifying half of these targets by interchanging the durational values of two to three sounds, while keeping the metre and the total number of sounds identical (as in Peretz and Morais, 1980; *see* C in fig. 2). The

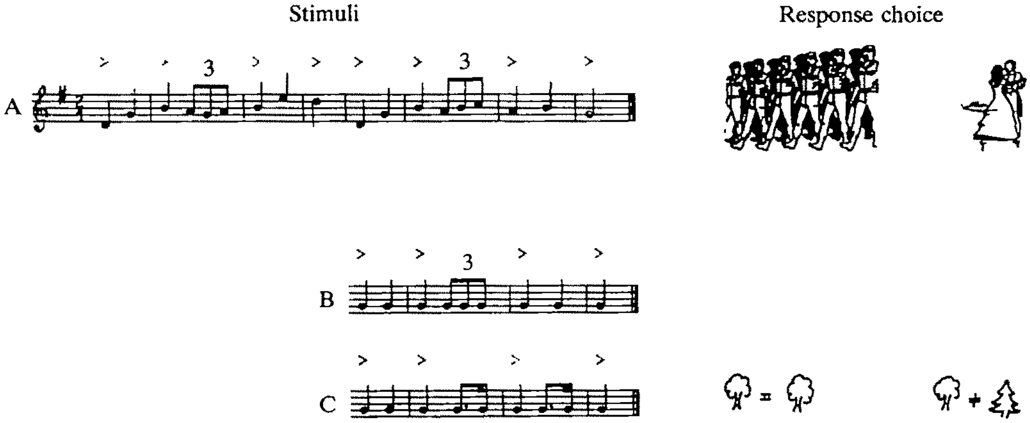

FIG. 2. Example of an entire initial melody (A) used in the metric task, its temporal reduction (B) used as a target and its transformation (C) used as a comparison in the rhythmic task. Symbols for response choice are also shown.

serial positions of these changes varied across patterns. Thus the only cue available for discrimination was the organization of relative durations of sounds and silent intervals (i.e., the rhythm).

A set of 2 practice and 24 experimental trials was constructed with these temporal patterns. In half of the trials, the target pattern was repeated (i.e., another rendition was recorded) after a 2 s silent interval and on the other half it was followed by its different comparison version. These two types of trials were recorded in a random order. In addition, within each trial, each temporal pattern was preceded by a warning signal in order to make clear the delination between target and comparison patterns.

Recognition tests. From the initial set of 24 second-phrase melodies, 10 were selected randomly for the recognition part of this study. Each of them had been presented four times in the same format (including the one embedded in the two-phrase sequences). Note, however, that presentation rate is far higher if the various transformations of these melodies (such as the contour-violated alternate or the tapped version) are perceived by the subjects as examplars of a central tendency corresponding to the initial melody itself (Welker, 1982). In addition to these 'old' melodies, a set of 10 recognition foils was prepared. These 'new' melodies were constructed along the same principles, but differed from the 'old' ones in their exact temporal and pitch pattern. These 20 sequences were then recorded in a random order.

Procedure

Subjects were run individually in a single session, with as many pauses between conditions as requested by the subject. They listened to the prerecorded tapes via a speaker placed on the table in front of them. The session began with a musical 'entrance', which consisted of 10 excerpts taken from commercial recordings. Their task was to judge whether or not they were familiar with the music presented. This test came from a larger set of excerpts that was originally designed to test familiar tune recognition. Since no patient ever failed to do well on this task (Delier, 1985; Duchatelet, 1986; and the same applied to the present study) and they all enjoyed doing it, a shorter version of this test was presented here in order to 'warm up' the subjects and to adjust the sound level, if necessary. Each subject was then presented either with the pitch organization conditions or with the temporal tasks. The order of presentation for these two main subtest categories was counterbalanced within each group. However, presentation order was fixed within the pitch organization conditions: all subjects were presented first with the contour-violated condition, then the contour-preserved condition followed by the transposed condition. This particular order, of increasing difficulty, was highly desirable, since performance level can be at floor for both the contour-preserved and the transposed condition when no familiarization with the task is provided. In contrast, order of presentation was counterbalanced for the two temporal tasks across subjects in each group. The session ended with the recognition test.

For all other conditions than the metric task and the recognition test, subjects were required to perform a 'same-different' classification task. They had to judge, on each trial, whether the target sequence and the comparison sequence were the same or not. For the transposed condition, the subjects were further instructed to disregard the fact that the melodies were played at different pitch levels, as if they were to judge a melody sung by a man was the same or not to a following melody sung by a woman (as in Peretz, 1987). Before each condition, 2 practice trials were presented and a symbol (*see* fig. 2) was used on the top of the response sheet to help in choosing the right answer. The practice trials were repeated until the subject indicated that he/she understood what was required from him/her. Subjects were then presented with the 24 experimental trials corresponding to the practice ones. No feedback on the accuracy of the responses was provided. Subjects responded by marking crosses with their unimpaired hand on the response sheet below the corresponding symbol.

For the metric task, subjects were informed that they would be hearing waltzes and marches, and that they had to discriminate them along that dimension. They had to mark a cross below the corresponding symbol (*see* fig. 2). Subjects were encouraged to tap along with what they perceived to be the underlying beat of each sequence. Feedback on the response was only provided on the 4 practice trials. Finally, for the recognition test, subjects were instructed that they would be hearing some of the tunes that they had been listening to during the session and that they would be mixed with new ones. Their task was to respond 'yes' if they recognized the tune and 'no' otherwise. This last test came as an incidental memory test, since subjects were not informed in advance that their memorization of the tunes would be tested later.

RESULTS

Pitch organization conditions

First, since there were twice as many 'different' as there were 'same' trials, the data obtained in each condition were examined in order to assess whether there was a bias to respond 'different'. If biased, subjects should make more errors on the 'same' trials than on the 'different' ones. In facts, subjects did exactly the opposite. All subject groups were found to make more errors on the 'different' than on the 'same' trials, in all three conditions (F(1,37)=45.53, $P < 0.001$); this tendency was found, however, to vary in size across groups (F(2,37)=7.53, $P < 0.002$). Scheffé post hoc comparisons indicated that this tendency to make more errors on 'different' trials was more marked in the RHD (61.5% vs 17.1% of errors, respectively) than in any other group (NC: 27.1% vs 11.1%; LDH: 37.3 vs 24.6%). As RHD were also the most impaired on these tests, it appears that the more errors the subjects make, the more likely they will respond 'same' rather than 'different'. In fact, such a negative correlation between the performance level and the tendency to make more errors on the 'different' trials was found to be general ($r=-0.74$, $P < 0.001$ across groups). This general pattern thus indicates that subjects were not biased to respond 'different' by the way the material was constructed. Rather they appear to have tried, and often failed, to differentiate the melodies.

The number of correct responses, obtained on both types of trials, was then submitted to an analysis of variance, including the three conditions as the within-subjects factor and the three groups as the between-subjects factor. A summary of the relevant data is presented in fig. 3. The analysis yielded an effect of Group (F(2,37)=19.31, $P < 0.001$), an effect of Condition (F(2,74)=41.40, $P < 0.001$) and an interaction between Group and Condition (F(4,74)=4.32, $P < 0.003$). The LHD group performed below the NC across all conditions, as shown by separate analyses (F(1,28)=9.68,

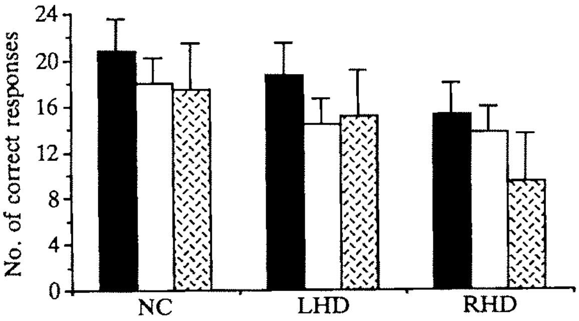

FIG. 3. Mean number of correct responses obtained for each pitch organization condition in each group. Filled areas = contour-violated; open areas = contour-preserved; hatched areas = transposed; NC = normal controls; LHD = left hemisphere damage; RHD = right hemisphere damage.

$P < 0.004$), but the LHD and the NC displayed the same pattern of response (there was no Group×Condition interaction, $F(2,56)=1.37$). Moreover, LHD as well as NC displayed sensitivity to the availability of the contour cue for discrimination, since they both performed significantly better on the contour-violated than on the contour-preserved condition ($F(1,28)=64.56$, $P < 0.001$; *see* fig. 3). The relative increase was similar across the two groups. The RHD did generally worse than the LHD group ($F(1,18)=7.03$, $P < 0.02$) but this depended on the condition. A Group×Condition interaction was found ($F(2,36)=6.46$, $P < 0.004$). Individual comparisons showed that LHD performed significantly better than RHD on the contour-violated and the transposed conditions ($F(1,18)=5.11$ and 21.47, respectively; $P < 0.04$) but did not differ on the contour-preserved condition ($F < 1$). Therefore, RHD appear to encounter particular difficulties in comparison with LHD when the melodic contour is available and/or necessary for discrimination. This result, suggesting an impairment in the use of the melodic contour by RHD, is also consistent with the observation that RHD, contrary to LHD and NC, did not exhibit a large increase of performance for the contour-violated over the contour-preserved condition ($F(1,9)=4.5$, $P=0.08$) and showed random performance (39.6% correct responses) on the transposed condition.

Because there was high variability in these conditions (*see* fig. 3), nonparametric tests were also performed on these data. The individual scores were ranked separately for each condition and then submitted to Kruskal-Wallis one-way analyses. For each condition, this statistical test yielded a significant result ($H=12.1$, $df=2$, $P < 0.01$ for the contour-violated condition; $H=12.3$, $df=2$, $P < 0.01$ for the contour-preserved condition; $H=21.0$, $df=2$, $P < 0.001$ for the transposed condition). Subsequent comparisons by way of Mann-Whitney tests indicated that the NC and the LHD differed on each condition (contour-violated condition: $U=46$, $P < 0.01$; contour-preserved condition: $U=54$, $P < 0.03$; transposed condition: $U=59$, $0.10 < P > 0.05$). The comparisons between the LHD and the RHD yielded the same pattern of significant differences as that obtained with the parametric tests. Their score distributions differed on the contour-violated and transposed conditions ($U=18$ and 7, respectively; $P < 0.01$) but did not differ on the contour-preserved condition ($U=45$).

When considering the lowest performance obtained by the NC as the cut-off point below which the scores obtained by brain-damaged patients can be regarded as indicating a genuine deficit, the pattern of results described above emerges even more clearly. For the contour-violated condition, 5 RHD but none of the LHD were found to exhibit a deficit. For the contour-preserved condition, 4 RHD and 3 LHD were so classified. And for the transposed condition, 3 LHD and all RHD but 1 were found to show a clear deficit. Following this classification criterion, individual data were examined in order to establish whether isolated deficits (i.e., dissociations) for one of the pitch organization conditions could be observed. Accordingly, one isolated deficit was found for the contour-preserved condition, but no isolated deficit could be found for the contour-violated condition. When a deficit was observed in the latter (in 5 cases), it was systematically associated with a deficit in both the contour-preserved and the transposed condition.

Further analyses were performed on the data obtained in the transposed condition as a function of contour cue. It should be recalled that, except for a change in pitch level on the target melodies, half of the differing comparison melodies were identical to the ones used in the contour-violated condition and half were identical to the ones of the contour-preserved condition. Distinguishing the responses between these two types of trials in the transposed set provides additional evidence regarding the use of contour as a discrimination cue. Note, however, that since RHD showed random performance, their data had to be excluded from this analysis. Nevertheless, the correct discrimination scores obtained by the LHD and the NC could be analysed in this way. A highly significant effect of Trial type was found: the NC obtained 79.4% correct and 58.1% for the contour-violated and the contour-preserved melodies, respectively, and the LHD 67.5% vs 51.3% correct ($F(1,28)=20.97, P < 0.001$). There was no interaction between Group and Type of trials ($F < 1$). Thus it is clear that when the contour was modified in the transposed melody, there was a very large increase in performance over the condition where this cue was not available. Both groups showed this effect, the relative increase being similar across groups.

Since the melodies were of varying length and incorporated a single pitch change in varying serial positions, they lent themselves to the examination of a memory short-term capacity effect in discrimination. In other words, long melodies with late pitch changes are expected to be more difficult to differentiate then short melodies with early changes, since the former require more information to be maintained active in working memory than the latter. Thus the present experimental conditions were appropriate to assess the functioning of short-term memory for pitch sequences, in particular in LHD patients who have been suggested to be impaired in this respect (Gordon, 1983). The data were found to be consistent with the idea that working memory contributed to the discrimination of melodies here. However, there was no evidence that LHD patients were differentially sensitive to this factor. The NC obtained 79.2% and 69.6% correct for discriminating short melodies with early changes and long melodies with late changes, respectively; the LHD performed with 70.6% and 58.3% correct and the RHD, with 56.6% and 43.3% correct, respectively. The variance analysis confirmed this overall distance effect ($F(1,37)=8.53, P < 0.005$), which did not depend on the group considered (there was no Group × Distance interaction, $F < 0.1$). The data obtained in the transposed set were not included in this analysis, since RHD performed at chance on this set and NC and LHD exhibited similar sensitivity to memory load with this set as with the reported untransposed sets. In the latter, 12 trials were considered as memory demanding since the number of intervening pitches between the first tone of the target melody and the modified tone was above 22 (mean=28), whereas in the 18 trials classified as less demanding the number of elapsed pitches was below 16 (mean=13). The correct responses obtained by each subject were analysed according to these two categories.

Temporal organization tasks

The mean correct scores obtained for each group for the 2 tasks involving temporal judgements are shown in fig. 4. The analysis of variance, including the three groups

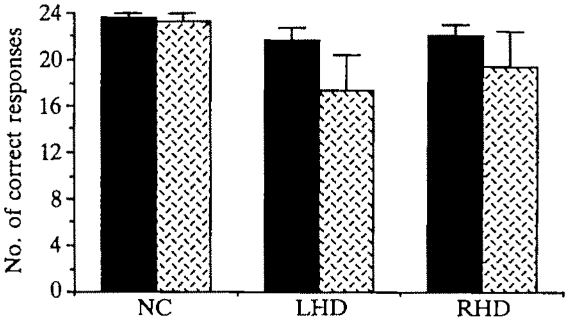

FIG. 4. Mean number of correct responses obtained for each temporal organization task in each group. Filled areas = metre; hatched areas = rhythm. Abbreviations as in fig. 3.

as the between-subjects factor and the 2 temporal tests as the within-subjects factor, yielded a significant effect of Test (F(1,37)=8.21, $P < 0.01$), the metre test being in general easier to perform than the rhythmic test and an effect of Group (F(2,37)=11.94, $P < 0.001$). There was also an interaction between Test and Group (F(2,37)=3.55, $P < 0.04$), which was due to the fact that the groups did not differ on the metre condition (F(2,37)=1.50) but did on the rhythmic condition (F(2,37)=17.11, $P < 0.001$). Both patient groups were found to differ significantly from the controls, but not from each other (NC vs LHD: F(1,28)=46.22, $P < 0.001$; LHD vs RHD: F(1,18)=1.44). These effects were confirmed by nonparametric tests. On the rhythmic condition, a main effect of group was obtained (H=27.6, df=2, $P < 0.001$) and comparisons between groups yielded the same results (NC vs LHD: U=0, $P < 0.001$; LHD vs RDH: U=32). However, when considering the lowest score obtained by NC on this task as the cut-off point, all 10 LHD patients were found to be impaired while only 5 of the RHD were found to exhibit a deficit. This suggests that there might be a difference between the LHD and the RHD but that either the size of the groups was too small or that the task was not sensitive enough (i.e., too easy) to make this trend statistically significant.

Far more subjects were initially tested on these specific tasks in a slightly different experimental context (Delier, 1985). The data of these additional subjects—14 LHD, 14 RHD and 28 matched NC—when combined with the ones reported here did show a very large effect of Group on the rhythm task (F(2,93)=18.27, $P < 0.001$) but not the slightest evidence of a side of lesion effect (LHD vs RHD: $F < 1$; 6 LHD and 8 RHD scored here below the cut-off point). Moreover, in these larger groups, clearer evidence for the dissociation between metre and rhythm was obtained. Indeed, 3 patients (2 LHD and 1 RHD) were found to perform at chance in the metric task (with 50%, 31.6% and 53.8% correct) but to perform in the normal range in the rhythmic task (with 100%, 79.2% and 95.8% correct, respectively). Thus the data collected here with a smaller group of patients seem to reflect a rather general pattern.

Nevertheless, it remains likely that even if LHD and RHD patients cannot be distinguished quantitatively, their respective impairment is not of the same nature.

However, no a priori hypothesis could be used to guide further examination of the data obtained in the present study, given the paucity of relevant information in the literature. Error distributions might still provide some insight in this respect and thus were plotted here for each brain-damaged group, although this inspection was not very instructive. Errors were found to be evenly and similarly distributed on the 'different' trials: the only distinguishing feature was found on the 'same' trials. On the latter, LHD made a few more errors than RHD. This more pronounced difficulty with identity decisions observed after a left hemisphere lesion might be related to their well-known fixation on irrelevant small deviations in material presentation. It should be recalled that the 'same' trials were made up of 2 different renditions of the same temporal sequence and thus involved slight surface variations.

Recognition test

The mean percentage of correct responses for the recognition test was 86.1, 69.4 and 70.6 for the NC, the LHD and the RHD, respectively. These scores were found to differ significantly (F(2,57)=7.81, $P < 0.001$). Both patient groups were found to be significantly impaired but did not differ from each other (NC vs LHD: F(1,28)= 12.77, $P < 0.001$; LHD vs RHD: $F < 1$).

Dissociations between the processing of pitch and temporal information

Inspection of the individual data of the patients led to the observation of cases of double dissociations between the processing of pitch patterns and the processing of temporal patterns. Evidence for a deficit in pitch organization was considered here by adding the scores obtained in the three pitch conditions and considering the lowest sum obtained by control subjects (i.e., 45/72 or 62.5% of correct responses) as the cut-off point. Alternatively, a deficit was considered to occur in temporal organization when performance was at chance (around 12/24) on the rhythmic task.

As indicated in the Table, 2 RHD were found to show a deficit in the processing of pitch information, while performing adequately on the temporal dimension. The reverse pattern of performance was found in 2 LHD, who performed at a normal level on the tests requiring consideration of pitch organization but failed on tests requiring temporal organization.

TABLE. PERCENTAGES OF CORRECT RESPONSES OBTAINED BY 4 BRAIN-DAMAGED PATIENTS FOR THE PITCH ORGANIZATION CONDITIONS AND FOR THE RHYTHMIC TASK AS WELL AS THE CORRESPONDING CUT-OFF POINTS

	Pitch organization	*Temporal organization*
V.G. (RHD)	36.1	91.7
V.C. (RHD)	58.3	95.8
L.N. (LHD)	70.8	54.2
C.V. (LHD)	75.0	41.7
Cut-off points	62.5	50.0

RHD = right hemisphere damage; LHD = left hemisphere damage.

DISCUSSION

The main aim of the present study was to assess in a unilateral brain-damaged population the idea supported essentially by data from normals that the left hemisphere is better equipped for dealing with local features of melody and the right hemisphere for arriving at global melody representations. The present findings are highly consistent with this view and further qualify the functional differences.

The treatments designed here to promote abstraction of global features in melodies varying along the pitch dimension consisted of (1) manipulating the availability of the melodic contour as a discrimination cue and (2) transposing one of the two melodies to be compared. If indeed subjects were using the contour in the melody comparison, as it has largely been demonstrated in other studies, they should display a substantial advantage for contour-violated melodies over contour-preserved ones and they should be able to discriminate melodies after transposition, in particular when these differ in their contour. Such evidence for the use of contour cue was found in both the NC and the LHD. In contrast, RHD were found to exhibit little sensitivity to the presence of contour as a discrimination cue and failed to discriminate reliably melodies after transposition. This pattern of results indicates that a lesion in the right hemisphere interferes with the possibility of representing and/or retrieving the contour of melodies.

In conditions where contour is not available for discrimination or when melody recognition is delayed, it is generally assumed that subjects rely on local melody features, such as the specific pitches or pitch intervals. Thus the use of local pitch information here was expected to be necessary in (1) the discrimination of the contour-preserved melodies and (2) the delayed recognition test. It was found that a lesion, whether in the right or left hemisphere, can impair local processing of melodies. Both LHD and RHD were equally impaired in those two conditions requiring consideration of local melody information. Such an impairment in processing the local aspects of melodies may account for the generally lower performance level observed in LHD in comparison with NC. The use of local information may contribute to some extent to all the conditions calling for pitch organization processes, particularly when familiarization with melodic material is provided.

Although unilateral brain damage in either hemisphere can affect the extraction of local pitch information, it may arise from different causes, as suggested in the Introduction. Following damage to the left hemisphere, the neural circuitry necessary for dealing with the local features may be disrupted while leaving intact that involved in building the global melody representation, which is apparently lateralized to the right hemisphere. In contrast, a right hemisphere lesion, by disrupting the processing subsystem required for representing the melody contour, may deprive the intact left hemisphere with the necessary anchorage points for encoding local information. The present pattern of results is highly consistent with this functional hierarchical relation between the hemispheres. Indeed, no isolated deficit could be observed on the contour-violated condition, which was systematically associated with deficits on the contour-preserved conditions, whereas an isolated deficit in the preserved-contour condition could be found.

This specific pattern of association and dissociation suggests that the processing of local intervals is dependent on intact contour processing. That the right hemisphere contributes to the provision of this contour representation onto which the left hemisphere processes can operate is attested by the fact that RHD were impaired in the use both of the interval and contour melodic information while LHD were impaired mainly in the use of interval information.

This particular notion of hierarchical cooperation between the hemispheres for processing the pitch dimension of melodies is consistent with most previous work, albeit not couched in these terms. For example (and *see* Peretz, 1985, for an extensive review of the literature along the present lines), a close examination of one of the most often cited studies in the area—that is, the study conducted by Milner (1962)—reveals a very similar pattern of results to the one observed here. She reported that on the Seashore tonal subtest, which involves judging which tone in a melody has changed in pitch on a second playing, patients who had undergone a right temporal lobectomy performed worse than those with a left temporal lobectomy. Nevertheless, the latter group was also found to perform below normal controls in this task, although this difference has not been assessed statistically. Thus, in that study as well as in the present study, it is apparent that damage to the right hemisphere leads to the most notable deficits but that the effect of damage to the left hemisphere is far from negligible. That damage to the left hemisphere can be very disruptive in tasks requiring consideration of local intervals, such as the one used in the Seashore battery, has been demonstrated to an even larger scale (by involving 90 LHD) in another study (Francès *et al.*, 1973). Such evidence for the involvement of the left hemisphere in listeners with little, or more often without any, musical education might pertain to the same class of left hemisphere processes that are used probably on a more routine (or mandatory) basis by musicians. This possibility would in turn explain the left hemisphere bias noted in the early case reports of amusias. However, to go beyond these deductive considerations requires more subtle consideration of the effects of brain damage on the musical perceptual abilities of proficient musicians than the ones traditionally pursued.

Yet, for the majority of listeners, the main conclusion of this part of the study is that cooperation of the two hemispheres is required to achieve efficient organization of pitch sequences, while admitting that a right-sided lesion is more disruptive to this function than one on the left. Moreover, it is likely that this function of pitch organization, and hence its neural implementation, is not limited to the processing of musical events but is involved in the discrimination of a variety of auditory events. The most straightforward domain to which the present conclusions might apply equally well is speech prosody. For example, analogies between intonation contours and melodic contours are striking, both at a descriptive and at a theoretical level (Thomassen, 1982; Dyson and Watkins, 1984). Thus, at a functional level, it is reasonable to assume the existence of a common device devoted to the processing of pitch contours in both speech and music. That this device might be subserved by a unique neural circuitry finds support in the fact that speech intonation contours have also been shown to trigger a right hemisphere mechanism (*see* Behrens, 1985, for a review).

Despite the apparent convergence between music and prosody, there remain many indeterminancies that may turn out to be critical for postulating similar principles of brain organization in the two domains. The major source of difficulty is that prosody is still largely a neglected area of investigation. Hence prosody, as a component of the linguistic system, has never been compared with melody as a component of the music system, beyond a very few theoretical considerations (*see* Lerdahl and Jackendoff, 1983, for one of the most extensive attempts). Moreover, in neuropsychology, when language and music functioning are compared, it is traditionally at the level of whole functions (Marin, 1982). Yet, it is the thrust of the present study that fractionation of whole functions into their elementary neural processing entities, that are assumed to differ in function, is necessary to understand the many diverse manifestations of hemisphere asymmetry. Accordingly, it is likely that comparison across domains will be most revealing once the relevant processing components have been identified in each domain. For the present, our study may be instructive. At the very least, it highlights the need to tease apart the pitch and temporal perceptual correlates of prosody which, to our knowledge, have not yet been considered.

In effect, all the above considerations arose from the results obtained by manipulating the pitch dimension of melodies. However, an attempt was also made in the present study to address similar questions, but in the temporal dimension. More specifically, investigation of the temporal properties was motivated, at least in part, by the idea that a local/global distinction might distinguish the relative competences of the hemispheres in the temporal domain as it did in the pitch domain. Accordingly, by assuming that the metre provides a global framework for encoding the precise rhythmic values, RHD were expected to be disrupted both in the metric judgement and rhythmic tasks, and LHD on the rhythmic task alone, as compared with normals. This hypothesis was partially supported, for both brain-damaged groups were found to be impaired on the rhythmic task. However, the metric test was successfully accomplished by most subjects.

That metre judgement was spared in the presence of disrupted rhythmic discrimination came as a surprise. Indeed, one of the most explicit models of temporal organization in music, that proposed by Povel (1984) and Povel and Essens (1985), assumes a hierarchical organization of these two temporal properties. Following this model, metre should be derived from rhythmic organization. More specifically, the first step would be to arrive at a rhythmic organization of the auditory sequence by hearing a succession of accented and unaccented events. The second step would be to map these temporal accents onto a beat framework that is used to build a metrical representation of the sequence. The fact that here a metrical representation could be built despite inadequate rhythmic representation of the sequence suggests that the processes responsible for arriving at these two types of representation are independent or at least not hierarchically organized as Povel proposes. It may be the case that the metric organization of a sequence is primary to and/or does not depend on rhythmic organization. The latter possibility is, in fact, considered in Lerdahl and Jackendoff's (1983) model of music mental representation. These authors view metre interpretation as a separate level of analysis that is not determined by the organization of relative durational tone values; the latter is governed by a distinct set of grouping rules. Therefore the present data can be viewed as fitting their model and hence as validating an alternative conception of temporal organization to the one proposed by Povel.

There is, however, an alternative explanation for the present findings that is compatible with both models. Here, in the metric task, subjects may have used nontemporal cues to come up with a metric interpretation of the sequences. Since the sequences presented were multi-dimensional, subjects may have relied on indications other than intensity accentuation or durational relationships. They may have used, for instance, the dynamic changes from tone to tone (through articulation and phrasing) or have looked for repeating pitch patterns (for a fuller discussion of these and other strategies, *see* Steedman, 1977, and Longuet-Higgins and Lee, 1982). Most of these indications were present in the material, and may have compensated for the disturbance in rhythm processing. Obviously, to settle this issue, further study will be required by isolating as much as possible the different cues relevant for metric organization.

In this respect, it should be emphasized that Povel's rules lend themselves to experimental work better than those of Lerdahl and Jackendoff, since the former are driven by the musical surface while the latter are essentially goal-oriented and thus depend largely on subjects' evaluation of the task. The present use of a 'waltz-march' classification task appears as a constructive step towards resolving this empirical difficulty, since it was found to successfully induce a metrical interpretation of the musical patterns. To show such effects in nonmusicians has sometimes been difficult (Smith, 1983; Monahan *et al.*, 1987), probably because the tasks used previously lacked ecological validity. Indeed, the fact that all listeners, irrespective of their training, can tap along and dance whilst listening to music demonstrates that they have, at least implicitly, some knowledge of the metric structure of the music. This implicit knowledge of metre seems to be easily accessed by tasks related to dancing activities, as the one used here. Thus by adding more control to the musical dimensions manipulated in the fragments presented in tasks requiring such 'dancing' judgements, it should be possible to evaluate if a metric representation is derived or is totally independent from temporal accent structure. These treatments should be the object of future research, for they will allow assessment of the neuropsychological validity of alternate current accounts of musical temporal organization.

Finally, one major finding of the present study concerns the observation of a double dissociation between the processing of pitch properties and the processing of temporal properties in musical sequences. Indeed, 2 cases with impaired abilities to deal with pitch properties were found to have spared temporal discrimination abilities. Conversely, 2 other patients were found to be severely impaired on the temporal processing of the sequences with preserved pitch organization abilities. From a neurological perspective, these 4 cases could not be distinguished by their lesion (in terms of location, depth and extent) from the rest of the patients. However, at a functional level, the finding of a double dissociation is important because it strongly suggests that pitch organization and temporal organization are processed by autonomous processing subsystems. This finding is not trivial, for there is currently a large debate on this issue in the field of cognitive psychology.

That the melody and rhythm of sequential patterns are integrated at some level in the process of music representation is unquestionable. Listeners are more accurate at discriminating embedded pitches that coincide with important temporal events (Jones *et al.*, 1982) and at transcribing melodies compatible in terms of pitch and temporal structure (Deutsch, 1980; Boltz and Jones, 1986). These effects can be attributed to a strategy of allocating attention to both components because this would optimize performance. Nevertheless, when decisional independence is promoted, that is, when the listeners are explicitly instructed to concentrate on one particular dimension at the expense of the other, they still exhibit patterns that are affected by the irrelevant dimension (Jones, 1987; Pitt and Monahan, 1987). Thus pitch and temporal organization appear at the very least intimately related. The fact that under other circumstances the two types of organization do not interact suggests that before integration they may have functional autonomy. Such independent effects have been reported for judgements of musical phrase completion (Palmer and Krumhansl, 1987*a*, *b*), for familiar tune recognition (White, 1960) and for similarity judgements (Halpern, 1984; Monahan and Carterette, 1985).

The problem with this issue is that perceptual independence is conceptually easy to formulate but problematic to apply, that is, to verify experimentally in normal subjects. Percepts are usually derived from responses that involve decisional evaluation, which can alter perception fundamentally, thereby making perceptual independence difficult to test (Ashby and Townsend, 1986). In all the above studies, the tasks used involved some kind of decisional evaluation or postperceptual judgement (judging similarity, sameness, and goodness) or have an important memory component (written recall, recognition). Therefore, listeners may well separate perceptually the two components in early stages of processing but must certainly integrate them somewhere in the later stages or in the decision-making process.

That pitch organization and temporal organization can be autonomous before integration is computed finds support in the behavioural dissociations observed here as a consequence of brain insult. The present finding of functional autonomy of the two subsystems can hardly be attributed to task parameters, that is to decision-making processes, since they were obtained with identical tests requiring 'same-different' classification responses. Thus the neuropsychological data argue strongly for the notion that melody and rhythm are subserved by independent subsystems, that depend apparently on different cerebral structure. However, these different anatomical locations should not be confounded with different hemispheres, despite the fact that the present data point towards that direction. Indeed, it does not seem that hemisphere differences are to be characterized along with musical dimension but rather along the local/global nature of the information to be abstracted. Depending on the level of structure manipulated, the results could have come out the other way round, at least for the pitch dimension. That is, if manipulation of pitch organization was limited to local features and the one applied to temporal organization to global ones (as yet remaining to be associated with the right hemisphere), a lesion in the left hemisphere could have produced a similar pattern to the one observed here after a lesion in the right hemisphere.

Whether localized in opposite hemispheres or not, the present finding of a double dissociation between pitch and temporal organization subsystems extends similar dissociations already reported in other spheres of musical behaviour to the perceptual domain. Although these earlier reports are somewhat anecdotal since they are essentially descriptive, they all point towards a dissociation between pitch and temporal phenomena in music. In singing, temporal variations can be preserved when pitch variations are impaired (Mann, 1898; Jossman, 1926, cited by Dorgeuille, 1966) and conversely, pitch variations can be spared when temporal variations are defective (Brust, 1980; Mavlov, 1980). In reading, the same picture emerges with selective impairment of the temporal variations (Dorgeuille, 1966; Brust, 1980) or of the pitch variations (Dorgeuille, 1966; Assal, 1973). Thus the current picture seems to be that throughout music processing the two musical dimensions can dissociate.

In conclusion, studying musical processing in brain-damaged nonmusicians provides important insights about the way the cerebral hemispheres cohere to provide a musical interpretation of the input. However, the current picture, while certainly encouraging, does not tell the whole story. Such an account is useful because it provides a precursor to building a theory as to how the brain interprets and transforms musical information. In particular, the present study provides clear support for the idea that music processing is too coarse a level of analysis; the function decomposes into several separate subabilities, which in turn are carried out by separate subsystems. Among these we can distinguish one system for processing pitch structure, which in turn must be further fractionated into two subsystems dealing with the melodic contour and the intervallic structure, respectively, and one for processing temporal variations. It is very likely that this number of processing subsystems will expand. Further progress in this field will be closely dependent on the advances of the research carried out in the cognitive study of music perception. As this latter domain is presently expanding rapidly, a more detailed account of hemisphere functioning for music should be forthcoming.

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LYME NEUROBORRELIOSIS

PERIPHERAL NERVOUS SYSTEM MANIFESTATIONS

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SUMMARY

An ever increasing number of apparently unrelated peripheral nervous system (PNS) disorders has been associated with Lyme borreliosis. To ascertain their relative frequency and significance, we studied prospectively 74 consecutive patients with late Lyme disease, with and without PNS symptoms: 53% had intermittent limb paraesthesiae, 25% the carpal tunnel syndrome, 8% painful radiculopathy, and 3% Bell's palsy; 39% had disseminated neurophysiological abnormalities. To assess the interrelationships among these syndromes, we reviewed the neurophysiological findings in all 163 such patients that we have studied to date. Reversible abnormalities of distal conduction were the most common finding. Demyelinating neuropathy was extremely rare. The pattern of abnormality was similar in all patient groups, regardless of whether the symptoms suggested radiculopathy, Bell's palsy, or neuropathy. We conclude that (1) reversible PNS abnormalities occur in one-third of our patients with late Lyme borreliosis, and (2) the pattern of electrophysiological abnormalities is the same in all and is indicative of widespread axonal damage, suggesting that these different presentations reflect varying manifestations of the same pathological process.

INTRODUCTION

Abnormalities of both the peripheral (PNS) and central (CNS) nervous systems are well recognized complications of infection with the tick-borne spirochaete, *Borrelia burgdorferi* (Garin and Bujadoux, 1922; Hellerström, 1930; Bannwarth, 1941; Dalsgaard-Nielsen and Kierkegaard, 1948; Schaltenbrandt, 1962; Bammer and Schenk, 1965; Hopf, 1975; Reik *et al.*, 1979; Wulff *et al.*, 1983; Pachner and Steere, 1985; Camponovo and Meier, 1986; Halperin *et al.*, 1987; Hirsch *et al.*, 1987; Kristoferitsch *et al.*, 1988). The triad of meningitis, cranial neuritis and painful radiculitis was initially felt to constitute the classical neurological syndrome associated with this disorder in North American patients (Reik *et al.*, 1979). Recent reports, however, have described a much broader range of PNS manifestations, including diffuse neuropathies (Camponovo and Meier, 1986; Halperin *et al.*, 1987), plexopathies (Pachner and Steere, 1985), a Guillain-Barré-like syndrome (Sterman *et al.*, 1982), and entrapment neuropathies (Halperin *et al.*, 1989). Although it was initially felt that these disorders usually occurred as part of an early, subacute phase of the illness, occurring several weeks to months after the initial rash

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and febrile illness, it is now clear that PNS disorders also occur as a manifestation of more chronic disease (Hopf, 1975; Halperin *et al.*, 1987).

As recognition of Lyme borreliosis and its neurological concomitants has increased, and as anecdotal descriptions of different PNS manifestations have proliferated, it has become difficult to determine from the literature the relative frequencies and significance of the myriad of different processes described. It also has become increasingly difficult to understand how such a large variety of different and apparently unrelated neurological syndromes could all be caused by the same infection. For these reasons, we have studied PNS function in a large number of patients with late Lyme disease. Previously, we have used neurophysiological techniques to characterize a mild, widespread and reversible neuropathy in these patients, a disorder marked by relatively mild signs and symptoms but definite abnormalities of nerve conduction and on nerve biopsy (Halperin *et al.*, 1987). We have now applied the same techniques in a prospective clinical and electrophysiological study of a large number of patients with late Lyme borreliosis. In this report, we describe the findings in 163 such patients in an effort to define better the types of abnormalities that occur.

MATERIAL AND METHODS

Diagnostic criteria

Patients were considered to have Lyme borreliosis if they (1) had had a well-documented, physician-observed rash consistent with erythema chronicum migrans (ECM, the pathognomonic cutaneous lesion of Lyme borreliosis (Steere *et al.*, 1977) and/or (2) had evidence of immunological reactivity against *B. burgdorferi*, measured either in a standard ELISA (Russell *et al.*, 1984), or in an assay of T cell immunity (Dattwyler *et al.*, 1988*b*) to this organism. Results of the ELISA, expressed as an optical density (OD), were only considered positive if the value obtained exceeded the mean OD of a simultaneously processed panel of normal controls by 3 SD or more. Patients also had other objective evidence of clinically active disease (usually active arthritis). Patients were considered to have 'late' (i.e., post-ECM) Lyme borreliosis if symptoms were ≥ 4 wks duration, measured from onset of the first sign or symptom.

Patients

Between May 1985 and December 1988, a total of 164 patients were evaluated (including the patients in the unselected group, Cohort 1). All were from areas highly endemic for Lyme borreliosis. Symptoms were chronic (≥ 4 wks duration) in all but 4; these 4 had more acute (1–3 wks) but severe neuropathy, without a clear antecedent tick bite or rash. Except for Cohort 1, these patients were highly selected and included many referred specifically for evaluation of neurological problems. Most of the patients were studied because they were thought to have neuropathy; 50 had minimal or no symptoms suggestive of PNS dysfunction (including 28 from Cohort 1). In each patient we attempted to determine the onset of infection, the onset of neurological symptoms, and the duration of disease at the time of evaluation.

Cohort 1. Between June 1986 and May 1987, 74 patients with late Lyme borreliosis were evaluated and followed by the Lyme Disease Service at the University Hospital, Stony Brook, New York. All were referred specifically for systemic or rheumatological symptoms; none was referred for neurological difficulties. Of these patients, 66 (Cohort 1a) were studied neurophysiologically (whether or not they had PNS symptoms); 8 declined (Cohort 1b). The characteristics of the studied patients, and of the 8 who were not studied, are outlined in Table 1. All 66 patients in Cohort 1a were examined by a neurologist and were screened for other disorders associated with neuropathies (investigations included blood glucose, VDRL, ANA, rheumatoid factor, thyroid function, and serum protein electrophoresis, all of which were normal).

Neurophysiological studies

Nerve conduction studies were performed using a TECA Mystro or DISA 1500 EMG apparatus in a shielded room, with ambient temperature maintained at approximately 22° C. Skin temperature was monitored and maintained above 33° C, using a servocontrolled heating apparatus (DISA). Using previously described techniques (Halperin *et al.*, 1987), we performed the following standard battery of tests in all but 4 of the patients (these 4 requested that the study be abbreviated): (1) unilateral motor conduction recording from (a) abductor pollicis brevis, stimulating the median nerve at the wrist and antecubital fossa; (b) abductor digiti minimi, stimulating the ulnar nerve at the wrist and proximal to the elbow; (c) extensor digitorum brevis, stimulating the peroneal nerve at the ankle and proximal to the fibular head; and (d) abductor digiti quinti, stimulating the tibial nerve at the medial malleolus and in the popliteal fossa; (2) F responses from each of these 4 nerves; (3) median, ulnar, radial and sural orthodromic sensory responses, on the same side as the motor responses; and (4) bilateral tibial H reflexes. Whenever the question of entrapment in the carpal tunnel arose, segmental (mixed) conductions were performed, comparing conduction in the palm-to-wrist vs palm-to-digit segments. Concentric needle EMG was performed when necessary. Blink reflexes were recorded in all patients studied before June 1987. Since this test never demonstrated clinically inapparent cranial nerve lesions in these patients, it was performed in only 12 selected patients studied after that date. All action potentials were recorded with surface electrodes. Motor terminal latency was judged to be normal or prolonged as a function of distance. Late response latencies were judged to be normal or prolonged as a function of the patient's height. In general, latencies, velocities and amplitudes were judged to be abnormal if they differed from the mean of our normals by at least 2 SDs. We also analysed the data using a more restrictive definition of abnormality. A nerve abnormality was considered 'major' if, in the absence of a focal entrapment, either (1) multiple different measures of nerve function were abnormal (e.g., sensory conduction velocity and motor amplitude in the same nerve) or (2) the abnormal values differed from the normal mean by 3 or more SDs. In Table 5, each column lists the total number of patients with the indicated abnormality, using both the more customary ('all') and the more restrictive ('major') criteria.

In 61 patients follow-up studies were performed after antimicrobial treatment (ceftriaxone 2 g/day i.v. for 14 days in virtually all patients), matching interelectrode distances exactly to those used at the initial assessment. Median time to retesting was 4 months (mean 5.9 months ± 5.4 SD, range 2–25 months.

Statistical methods

Neurophysiological data were analysed in two different ways. First, we determined the number of different nerves with demonstrable abnormalities for each patient (e.g., if median motor and sensory conduction were both abnormal, this was counted as a single abnormal nerve). Those with significant abnormalities of 2 or more different nerves, excluding focal entrapments, were felt likely to have a neuropathy. Secondly, for each patient we calculated mean values for each of the following: motor terminal latency, conduction velocity (CV), and amplitude, and F wave latency (mean of median, ulnar, peroneal and tibial nerves); sensory CV and amplitude (median, ulnar, radial and sural nerves); H latency (2 tibial nerves); and blink R1 and R2 latencies. In the 61 patients who were restudied following antimicrobial therapy, pre- and posttreatment mean values for each individual (mean motor terminal latency, CV, etc.) were compared, using Student's 2-tailed t test for paired data.

ILLUSTRATIVE CASE HISTORIES

Radiculitis and Bell's palsy

A 64-yr-old right-handed man was bitten by an insect in May 1987, while on Fire Island, NY (an area highly endemic for Lyme borreliosis). He developed a bullseye-shaped rash on his left hip, evolving to encompass his entire trunk. Although afebrile, he began to feel exhausted with diffuse aches and pains. He borrowed his neighbour's blood glucose tester and found himself to be hyperglycaemic for the first time in his life. Although he was started on oral hypoglycaemic drugs he felt no better. Three weeks after the bite, he developed severe electric shock-like pain, radiating down the left leg to the foot. This persisted, and 3 wks later he developed Bell's palsy on the left. With this he noted difficulty tasting, and increased sensitivity of his left ear to noise. His systemic symptoms worsened for 4 wks until he was diagnosed as having Lyme borreliosis (ELISA OD 0.791, negative cut-off 0.119), and was treated with oral penicillin. His malaise and hyperglycaemia resolved, but he noted residual weakness of the left leg, abdominal numbness, and arthralgia without arthritis. Neurological examination demonstrated completely normal cranial nerve function, excellent strength except for difficulty walking on heels due to weakness of dorsiflexion of the left foot, mild bilateral decrease in vibration sense, and normal tendon reflexes except for a markedly decreased left ankle jerk. Nerve conduction studies demonstrated a low amplitude tibial motor response on the left (1.5 mV) with a delayed F response (67 ms, 3 SDs = 62.4 ms), a low amplitude radial sensory potential (2.8 μV), slow ulnar sensory conduction (43 $m \cdot s^{-1}$), a delayed tibial H reflex on the right (39.9 ms) and an absent response on the left (3 SDs = 34.5 ms). He was treated with i.v. ceftriaxone and recovered.

Bell's palsy

In May 1988, this 37-yr-old right-handed woman developed difficulty tasting on the right, rapidly followed by right facial weakness. This was treated with a brief course of corticosteroids, and rapidly resolved. She did well until August 1988, when she noted progressive migratory arthralgia, followed by difficulty tasting on the left, succeeded rapidly by a left Bell's palsy. Hearing was not affected with either episode. She had no headache. Neurological examination demonstrated an incomplete left seventh nerve paresis but otherwise normal cranial nerve function, normal sensation, strength, gait, cerebellar and cognitive function, and normal tendon reflexes except for mildly diminished left biceps and triceps jerks. CSF examination demonstrated 10 monocytes, 1 erythrocyte, protein 0.32 g/l, glucose 2.9 mmol/l (simultaneous serum glucose 4.5 mmol/l), IgG index 0.76 (normal < 0.70), and no oligoclonal IgG bands. Lyme serology was positive (OD 1.319, negative cut-off 0.122). Nerve conduction studies demonstrated bilateral low amplitude facial nerve motor responses (0.9 mV on the left, 1.8 on the right), absent left-sided responses on blink reflexes, bilaterally absent tibial H reflexes, and a prolonged right peroneal motor terminal latency (6.6 ms, 3 SDs for distance 5.8 cm). She was treated with i.v. ceftriaxone (2 g/day, 14 days) and recovered completely over 1 month.

Paraesthesiae

This 37-yr-old woman was in excellent health until May 1985, when she developed a ring-shaped rash on her right arm, following which multiple similar ring-shaped lesions appeared over her entire arm. This resolved spontaneously over about 6 wks. By the time the rash had disappeared, the patient noted the onset of fatigue, low-grade fever, and near constant numbness and tingling of the hands (occasionally nocturnal), and to a lesser extent the feet. Evaluation in December revealed a positive Lyme serology (OD 0.134, negative cut-off 0.104). Neurological examination was completely normal except for a mild, symmetric bilateral decrease in vibration sense in the feet. Nerve conduction studies demonstrated prolonged median motor terminal latency (4.5 ms, predicted for distance 4.2 cm), and slowed median (40 $m \cdot s^{-1}$) and radial (44 $m \cdot s^{-1}$) sensory conduction velocities. Segmental median conduction studies demonstrated bilateral entrapments in the carpal tunnels. The peroneal F response was substantially prolonged (latency 66.8 ms, predicted 3 SDs 53.4 ms). Following treatment with 1 month of oral penicillin, her sensory symptoms decreased; repeat neurophysiological testing 5 months later demonstrated normalization of all abnormalities except those referable to the entrapment in the right carpal tunnel.

RESULTS

Patients in Cohort 1 appeared demographically comparable with the overall group of patients studied (Table 1). This subset was studied to determine the relative frequency of different PNS abnormalities. This cohort was biased to under-represent neurological disease—only patients referred to a rheumatology-based Lyme Disease Clinic were included. Any patient whose initial symptoms were primarily neurological—such as Bell's palsy or painful radiculitis—would have been less likely to have been included in this study. Within this group, there were no significant demographic differences between the 66 patients who were studied and the 8 who were not. Of the 74 patients in this group, 40 (54%) reported intermittent paraesthesiae. Of the 66 who underwent neurophysiological testing, 26 (39%) had abnormalities of 2 or more nerves. Since we have previously noted that the carpal tunnel syndrome occurs in about 25% of patients with late Lyme borreliosis (Halperin *et al.*, 1989), we also reanalysed the data, eliminating abnormalities attributable to this entrapment: 20 patients (30%) still had abnormalities of 2 or more nerves. When we restricted the range of abnormalities further, excluding focal entrapments, and including only 'major' abnormalities (i.e., those differing from the normal mean by 3 SDs or more, or those in which several independent abnormalities were noted in the same nerve), 9 patients (14%) still had evidence of a diffuse, otherwise unexplained neuropathy.

TABLE 1. PATIENT CHARACTERISTICS—SUBGROUPS

	Cohort 1a (1986–1987) studied	*Cohort 1b (1986–1987) not studied*	*All*
Number	66	8	163
M/F	28/38	4/4	79/84
Age* (yrs)			
Mean ± SD	39.9 ± 12.0	48.1 ± 18.9	42.0 ± 14.4
Range	14–77	19–77	9–82
Duration (mos)*			
Median	12		12
Mean ± SD	29.4 ± 42.4	24.2 ± 37.6	26.5 ± 36.5
Range	1 m–18 y	6 w–11 y	1 w–18 y
Paraesthesiae**	38	2	90
No. with ≥ 2 abnormal nerves	26		77
CTS eliminated	20		68
Major, no CTS	9		39

* Differences in age, sex and duration of illness not statistically significant (Student's 2-tailed t test). ** Proportion with paraesthesiae (Cohort 1, patients studied vs not studied) not statistically significantly different (Fisher's exact test). CTS = carpal tunnel syndrome.

The most common symptom described by patients with neuropathy was the presence of intermittent limb paraesthesiae, affecting the upper or lower limbs or both (Table 2). These paraesthesiae were most commonly distal in the limb, but were also reported by a few patients in a more patchy distribution. Clinical sensory examination of these

TABLE 2. PATIENT CHARACTERISTICS—ALL PATIENTS

	Asymptomatic	*Paraesthesiae*	*Radiculopathy*	*Bell's palsy*
Number	50	90	17	8
Age				
Mean (yrs, SD)	38.5 (15.6)	44.1 (13.8)	42.6 (13.7)	45.3 (14.2)
Range	9–82	16–77	16–71	24–71
Duration (mos)				
To symptom onset				
Median		6	5	2
Mean (SD)		22.5 (33.8)	16.8 (26.7)	4.8 (7.4)
To evaluation				
Median		12	9	3
Mean (SD)	29.5 (44.6)	27.4 (34.0)	17.1 (23.3)	12.4 (10.9)
No. of normal studies	30	20 $P < 0.0005$*	4 $P = 0.01$**	0 $P = 0.0017$
No. of abnormal nerves				
Mean (SD)	0.7 (1.1)	2.6 (2.3) $P < 0.001$***	1.9 (1.9) $P < 0.05$***	4.0 (1.6) $P < 0.001$***
No. of patients with $\geq$ 2 abnormal nerves	8	55 $P = 0.00005$**	8 $P = 0.014$**	8 $P = 0.00006$**
No. with CTS	4	31	3	3
Eliminating CTS				
No. of abnormal nerves				
Mean (SD)	0.7 (1.1)	2.3 (2.2)	1.7 (2.0)	3.8 (1.7)
No. of patients with $\geq$ 2 abnormal nerves	8	48 $P = 0.00006$**	7 $P = 0.039$**	7 $P = 0.0002$**
Also eliminating minor abnormalities				
No. of abnormal nerves				
Mean (SD)	0.3 (0.9)	1.4 (1.9) $P < 0.001$***	0.7 (1.2) n.s.	2.1 (1.4) $P < 0.01$
No. of patients with $\geq$ 2 abnormal nerves	3	29 $P = 0.0002$**	4 n.s.	5 $P = 0.003$**

* χ^2; ** Fisher's exact test; *** Student's 2-tailed t test; each group compared with the first, asymptomatic population; CTS = carpal tunnel syndrome.

patients generally demonstrated minimal if any distal sensory loss (exclusive of findings due to the carpal tunnel syndrome). The mean number of nerves abnormal in patients with paraesthesiae was significantly greater than among those without, even if abnormalities due to the CTS were eliminated, and even if only 'major' abnormalities were included. Sensory conduction velocities and amplitudes (Tables 3, 5), and motor terminal latencies (Tables 4, 5) were the values most likely to be affected; late response latencies were also frequently abnormal. Blink reflexes were rarely abnormal, and in fact never demonstrated abnormalities which were not clinically evident. When patients were retested following antimicrobial therapy, the improvements in sensory amplitude and CV, and motor terminal latency, were all highly significant (Table 6). F response latencies also improved significantly.

Seventeen patients had pain that was radicular in character; this involved an arm in 3, the trunk in 1, and a leg in 13. The site of radicular symptoms bore no consistent relationship to the site of the tick bite. Neurophysiological studies in these 17 patients

TABLE 3. SENSORY CONDUCTIONS AND H REFLEX

		Median		*Ulnar*		*Radial*		*Sural*		*Tibial H reflex (ms)*	
		Amp.	*CV*	*Amp.*	*CV*	*Amp.*	*CV*	*Amp.*	*CV*	*L*	*R*
Normal		≥5 μV	≥47 m·s⁻¹	≥5	≥44	≥5	≥46	≥5	≥34		
Major		≤3	≤41	≤3	≤39	≤3	≤40	≤3	≤29		
Case	*Age (yrs/sex)*										
Paraesthesiae											
P1	55M	5.0	**44**	5.0	**44**			*3.0*	43	32.8	32.0
P2	30M	8.0	52	7.0	51			**4.0**	45	*Absent*	*Absent*
P3	69F	*Absent*		*Absent*		11.4	48	*2.4*	42	*36.2*	*35.3*
P4	37F	11.0	*40*	7 0	**46**	8.0	**44**	11.0	45	27.3	26 8
P5	59M	8.0	*40*	5 0	*36*	10.0	45	5 0	52	27.8	28.6
P6	47M	11.0	**44**	6.0	**44**			*3.0*	41	30.9	29.7
P7	33M	10.0	**46**	7.0	**46**			**4.0**	38	*Absent*	*Absent*
P8	39M	10.6	**44**	9.2	55	**4.9**	56	7.5	55	*Absent*	*Absent*
P9	62M	8.8	58	**4.5**	62	7.0	61	*Absent*		35.9	*40.3*
P10	39M	10.8	*34*	5.7	49	12.4	50	5.8	49	27.7	28.4
P11	20M	12.4	49	10 0	45	9.2	52	*2.9*	40	31.1	30.7
P12	47F	*0.6*	*32*	*2.8*	46	**3.9**	54	*Absent*		33.9	31.2
P13	65F	6.8	50	7.6	51	8.8	52	9.0	44	*34.0*	*35.0*
P14	68F	6.0	*39*	**4.0**	45	*3.0*	*37*	*Absent*		33.7	*Absent*
P15	55M	13.6	51	6.8	49	13.4	51	6.8	41	*Absent*	*Absent*
P16	59F	*Absent*		*Absent*		*Absent*		*Absent*		*Absent*	*Absent*
P17	56M	11.0	56	7.0	53	14.0	47	12.0	42	30.6	30.7
P18	54M	7 0	47	3.2	50	*2.4*	54	**4.5**	51	**34.5**	**34.0**
P19	51M	7.2	*38*	7.4	**41**	16.0	*38*	7.8	42	**31.2**	28.9
P20	59M	**4.2**	51	*1.3*	45	7.8	52	*Absent*		32.9	33.5
P21	74F	14.4	59	11.2	52	23.0	51	5.4	53	*Absent*	*Absent*
P22	53M	*Absent*		*Absent*		*Absent*		*Absent*		*Absent*	*Absent*
P23	65M	*2.8*	33	*Absent*		**4.2**	49	*Absent*		31.7	32.2
P24	59M	8.6	*36*	*Absent*		*Absent*		*Absent*		32.0	32.3
P25	77M	6.2	**44**	**3.5**	*44*	5.0	44	*Absent*		*Absent*	*Absent*
P26	70M	7.4	*40*	*2.6*	53	**4.2**	48	7.0	46	*38.6*	*39.2*
P27	47M	6.0	47	7.0	49	8.0	47	*2.0*	48	30.0	*Absent*
P28	23M	14.0	*40*	12.4	**41**	8.4	**45**	8.2	51	*Absent*	*Absent*
Bell's palsy											
B1	40M	9.0	51	7.6	47	10.2	47	*2.7*	47	31.7	31.6
B2	41M	8.3	**43**	4.7	41	11.0	**43**	13.4	42	30.6	32.4
B3	37F	32.0	**58**	22.0	51	22.0	55	21.0	55	*Absent*	*Absent*
B4	64M	5.8	**46**	6.0	**43**	*2.8*	53	6.0	40	*Absent*	*39.9*
B5	71M	7 8	*43*	4 7	52	6.4	56	**4.2**	46	**35.4**	33.9
Radiculopathy											
R1	48M	10.0	49	4.0	**41**	5.0	53	8.0	**40**	*Absent*	29.3
R2	71M	7.8	*43*	4.7	52	6.4	56	**4.2**	46	**35.4**	33.9
R3	47F	13.2	62	9.2	51	24.4	53	12.2	51	*Absent*	29.3
R4	64M	5.8	46	6.0	**43**	*2.8*	53	6.0	40	*Absent*	*39.9*

Abnormal results in bold face; major abnormalities italicized; Amp = amplitude; CV = conduction velocity.

demonstrated the same type and range of abnormalities seen in all other symptomatic patients (Tables 3–5). Sensory conduction was abnormal in 9, a finding that should not be present in lesions restricted to the nerve roots. In 7 there were neurophysiological abnormalities in nerves remote from the involved limb. In 8 patients, radicular symptoms resolved completely following antimicrobial therapy; recovery was incomplete in the others.

Facial palsy occurred in 8 patients. All had neurophysiological abnormalities of other nerves as well. This group had the greatest mean number of abnormal nerves of any of the 4 patient subgroups: 6 had abnormal sensory conduction. The Bell's palsy generally began to improve even before antibiotics were started. After treatment, clinical recovery was complete in all (although mild abnormalities of blink reflex latencies tended to persist).

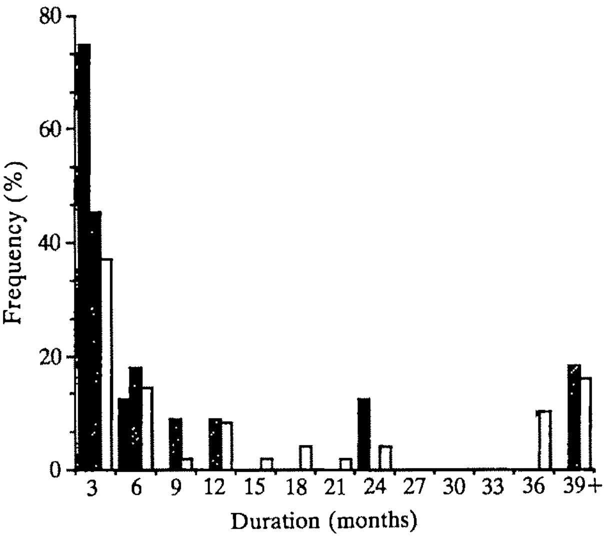

FIG. Distribution of disease duration (first symptom to onset of neurological symptoms) for patients with Bell's palsy, radiculitis, and paraesthesiae. Closed columns = Bell's palsy (n = 8); hatched columns = radiculitis (n = 11); open columns = paraesthesiae (n = 49).

Duration of disease before the onset of neurological symptoms was briefest in patients with Bell's palsy (median 2 months), but essentially the same in patients with radiculitis (median 5 months) and paraesthesiae (median 6 months). Moreover, the temporal distribution of onset of symptoms in patients with the latter two syndromes was quite comparable (*see* fig.). In contrast, the overall duration of disease (from time of infection to time of evaluation) was considerably longer in patients with paraesthesiae (median 12 months compared with 9 months in patients with radiculitis, and 3 months for Bell's palsy).

Median nerve entrapment in the carpal tunnel was demonstrated in 17 patients in Cohort 1 and in 37 patients overall; none has required surgical treatment. Only 1 patient had a plexopathy—a 40-yr-old man developed a left brachial plexopathy; he recovered well following antibiotics.

Two patients have had a more severe and acute neuropathy, clinically initially felt to be suggestive of acute inflammatory demyelinating polyneuropathy (AIDP). One, a 59-yr-old woman (Case P16), developed rapidly progressive weakness 2 wks after a flu-like illness. There was no known antecedent tick bite or rash. The CSF protein was 1.53 g/l; there were 2 WBC/μl. Nerve conduction studies demonstrated widespread extreme slowing of motor CV ($<$ 60% normal mean) (Buchthal *et al.*, 1984), extreme prolongation of motor terminal latencies ($>$ 2× normal) (McLeod *et al.*, 1973), marked prolongation of late responses, and absent sensory potentials. No specimen was obtained for Lyme serodiagnosis initially, and she was treated with plasmapheresis, with an excellent clinical recovery. On follow-up 3 months later her serum was positive

TABLE 4. MOTOR CONDUCTIONS

	Median				*Ulnar*				*Peroneal*				*Tibial*			
	Amp.	*TL*	*CV*	*F*	*Amp.*	*TL*	*CV*	*F*	*Amp.*	*TL*	*CV*	*F*	*Amp.*	*TL*	*CV*	*F*
Normal	>4 mV	ms	≥48 m·s⁻¹	ms	≥3.5	ms	≥49	ms	≥2.8	ms	≥40	ms	≥3.9	ms	≥41	ms
Major	<3		≤43		≤2.5		≤44		≤1.8		≤34		≤3.0		≤37	
Case																
Paraesthesiae																
P1	17.0	3.8	52	31.7	10.0	2.1	53	30.3	7.0	*7.0*	46	*60.7*				
P2	12.0	3.4	59	24.9	10.0	3.1	67	26.6	4.0	*5.8*	60	52.8	12.0	5.9	43	52.1
P3	8.0	3.9	49	**31.9**	4.5	3.7	**39**	**32.0**	*1.0*	4.9	42	*54.8*				
P4	**3.0**	**4.5**	66	24.6	8.5	**3.6**	63	24.4	3.0	4.5	46	*66.8*				
P5	8.0	3.9	55	27.8	8.5	3.5	64	26.0	8.5	*6.0*	59	46.5				
P6	11.0	**4.7**	58	*Absent*	9.5	3.1	52	31.0	7.5	4.8	57	**55.0**				
P7	17.0	*4.8*	54	31.6	12.0	3.2	55	*39.4*	8.0	5.3	46	42.0	*Absent*			*Absent*
P8	7.1	3.9	56	29.9	8.4	2.9	56	30.3	4.6	3.6	46	46.2	4.6	4.8	47	47.7
P9	9.0	3.3	53	32.0	6.2	2.8	56	32.4	**2.1**	4.6	45	*64.6*	*2.0*	5.9	45	*65.1*
P10	11.7	*4.8*	53	28.9	11.8	3.3	54	29.1	4.8	*6.7*	51	52.5	**3.0**	6.4	45	49.5
P11	9.1	**4.6**	56	29.4	10.5	3.6	60	29.9	3.5	*7.3*	42	**59.5**	. 4.6	8.2	43	58.1
P12	10.2	*5.1*	51	**31.9**	10.2	3.2	51	29.8	6.2	3.5	51	47.9	*Absent*			
P13	6.3	3.8	50	**28.5**	8.4	2.6	55	26.3	3.4	*6.3*	56	**54.4**	**3.6**	6.9	43	51.2
P14	8.0	4.2	52	26.0	11.0	3.1	50	26.0	*1.5*	7.2	42	*51.5*	5.5	6.8	47	51.6
P15	13.6	3.6	57	31.7	12.6	3.0	57	31.4	9.3	4.9	46	54.3	6.1	5.8	42	56.0
P16	*1.3*	*11.1*	*37*	*39.6*	*1.4*	*4.9*	57	*42.6*	*0.1*	*13.2*	*23*	*Absent*	*Absent*			
P17	8.0	3.7	53	26.7	9.0	3.1	53	25.8	**2.5**	*6.7*	39	53.8	*2.5*	4.8	41	47.9
P18	11.5	4.1	50	**32.9**	8.2	2.8	51	30.0	**2.6**	4.5	40	*Absent*	*0.4*	6.5	56	**58.0**
P19	4.7	*5.4*	53	**28.4**	10.3	2.4	55	26.0	6.7	*5.7*	49	49.4	9.4	6.6	45	50.7
P20	9.6	4.1	53	29.0	10.1	3.1	51	28.9	5.4	4.6	42	**58.0**	8.0	7.7	43	*62.7*
P21	15.6	3.0	54	26.8	6.3	2.7	54	26.1	**2.2**	3.2	45	50.5	5.6	5.3	50	54.9
P22	8.1	**4.3**	48	31.0	5.2	**3.7**	49	30.0								
P23	9.0	*4.9*	48	31.1	*1.4*	*4.2*	49	30.2	*0.7*	4.9	48	*57.4*	*2.0*	6.1	49	**55.2**
P24	6.3	*5.1*	51	30.8	*0.4*	*4.3*	*30*	**33.5**	*1.0*	4.5	43	50.5	*0.4*	5.9	42	*Absent*
P25	11.3	*4.7*	55	26.1	9.8	3.4	50	*30.4*	*0.3*	*7.2*	*34*	*Absent*	*0.5*	*7.2*	*37*	*Absent*
P26	14.0	**4.4**	52	*34.8*	10.5	2.9	52	**33.0**	4.3	4.9	**39**	45.0	*1.0*	6.3	42	*63.7*
P27	13.0	3.1	55	27.2	13.0	3.0	55	28.3	6.0	5.3	50	**54.2**				
P28	4.4	3.5	53	**31.8**	3.8	2.7	67	31.1	*1.1*	4.4	48	**55.3**				
Bell's palsy																
B1	8.5	**4.4**	57	31.2	11.0	3.8	57	29.7	6.2	**5.4**	39	55.2	11.4	7.6	42	*62.5*
B2	7.3	**4.5**	**45**	**32.5**	7.0	3.9	51	**32.5**	3.7	4.1	40	**57.3**	8.4	6.7	41	59.8
B3	17.0	2.8	58	24.0	12.0	2.5	55	24.1	8.0	*6.6*	65	45.9	7.0	5.5	45	48.5
B4	13.2	4.0	55	31.0	8.1	3.2	57	31.2	6.1	5.4	42	**59.0**	*1.5*	6.5	42	*67.0*
B2	10.0	*4.8*	57	*Absent*	8.8	2.8	**47**	**32.5**	3.7	4.0	43	54.9	*2.4*	6.5	49	**58.4**
Radiculopathy																
R1	12.0	3.7	57	26.4	5.5	3.2	61	26.2	8.0	3.2	50	46.3				
R2	10.0	*4.8*	57	*Absent*	8.8	2.8	**47**	**32.5**	3.7	4.0	43	54.9	*2.4*	6.5	49	**58.4**
R3	15.8	3.0	56	24.4	9.5	2.1	57	25.4	6.0	3.2	47	47.3	*2.8*	4.8	43	50.9
R4	13.2	4.0	55	31.0	8.1	3.2	57	31.2	6.1	5.4	42	**59.0**	*1.5*	6.5	42	*67.0*

Abnormalities in bold face, major abnormalities italicized; Amp. = amplitude; TL = terminal latency; CV = conduction velocity; F = F responses.

TABLE 5. NERVE CONDUCTION ABNORMALITIES

	Asymptomatic *All/major**	*Paraesthesiae* *All/major**	*Radiculopathy* *All/major**	*Bell's palsy* *All/major**
Number	50	90	17	8
Sensory				
Amplitude	10/2	35/16	5/2	5/2
Conduction velocity	4/0	38/20	7/2	4/2
Amp. or CV	13/2	53/29	9/4	6/4
Amp. or CV, excluding CTS	10/2	40/22	6/3	5/3
Motor				
Terminal latency	5/2	42/31	4/3	4/2
Terminal latency excluding CTS	4/1	29/24	2/0	3/2
Amplitude	3/2	34/19	3/3	3/2
Conduction velocity	1/1	7/3	3/0	1/0
F responses	8/0	42/18	6/2	6/3
H reflexes	5/3	23/15	5/3	3/2

*All abnormalities/minor abnormalities and entrapments eliminated.

TABLE 6. NEUROPHYSIOLOGICAL RESPONSE TO TREATMENT

	Pretreatment		*Posttreatment*		
	Mean	*SD*	*Mean*	*SD*	
Number = 61					
Interval between studies (mos)					
Median				4	
Mean				5.9	
SD				5.4	
Sensory conduction					
Amplitude (μV)	10.8	(4.3)	12.7	(4.4)	$P < 0.001$*
Conduction velocity ($m \cdot s^{-1}$)	49.6	(4.7)	51.8	(4.2)	$P < 0.001$*
Motor conduction					
Terminal latency (ms)	4.2	(0.56)	4.05	(0.55)	$P < 0.025$*
Amplitude (mV)	8.5	(1.9)	8.9	(1.9)	
Conduction velocity ($m \cdot s^{-1}$)	52.1	(4.4)	52.6	(3.6)	
H reflex latency (ms)	30.1	(2.4)	29.7	(2.3)	
F wave latency (ms)	37.9	(4.0)	37.3	(3.8)	$P < 0.01$*
Blink reflex latencies	No significant changes				

* Student's 2-tailed t test for paired data.

for anti-Lyme antibody (OD 0.105, negative cut-off 0.101); at that time she was asymptomatic. In only 1 of the other 162 patients have neurophysiological studies demonstrated extreme conduction slowing, extreme prolongation of motor terminal latencies, or any evidence of conduction block.

The other patient who was initially thought to have AIDP was a 23-yr-old man (Case P28) who developed rapidly progressive weakness over a 1 wk period, associated with severe headaches, fever, lethargy, and meningism. His CSF contained 374 WBC/μl (90% lymphocytes, 10% neutrophils), protein 1.05 g/l, normal glucose concentration and negative cultures. Serum and CSF were both positive for anti-*B. burgdorferi* antibodies. Nerve conduction studies demonstrated a moderate decrease in motor response amplitudes, normal motor conduction velocities and terminal latencies, mild slowing of sensory CV, mildly prolonged F wave latencies, and absent H reflexes. Following antimicrobial therapy, he improved clinically and neurophysiologically.

The question as to whether the neuropathy in these 2 cases was related to Borrelia infection is considered in the Discussion.

DISCUSSION

Peripheral nervous system involvement in Lyme borreliosis is extremely common (Wulff *et al.*, 1983; Pachner and Steere, 1985; Halperin *et al.*, 1987; Hirsch *et al.*, 1987; Vallat *et al.*, 1987; Kristoferitsch *et al.*, 1988). In this study we have attempted to define the range of abnormalities that occurs. As others have noted, Bell's palsy and painful radiculitis (Reik *et al.*, 1979; Pachner and Steere, 1985) occur frequently in patients with Lyme borreliosis. In the prospectively studied, unselected cohort of 74 patients (Cohort 1), 2 (3%) had Bell's palsy, and 6 (8%) had radicular pain. Since this population was somewhat biased against detecting syndromes that were primarily neurological, this may under-represent the true incidence, although these values are actually quite similar to the 10% combined incidence commonly referred to in the literature (Pachner, 1986). However, far more common in our population has been a diffuse but relatively mild peripheral neuropathy. Of the unselected patients, 54% described intermittent paraesthesiae, usually distal in distribution, but sometimes quite patchy; 39% of those studied had neurophysiological evidence of a diffuse neuropathy. The presence of paraesthesiae correlated very strongly with evidence of neuropathy.

Although these observations would seem to confirm the impression that Lyme borreliosis causes a wide variety of distinct and unrelated PNS syndromes, a closer examination of our data suggests that these differences may be more apparent than real. First, we have found that, although the observed abnormalities are readily reversible, only rarely do the neurophysiological data suggest that the disorder is demyelinating (the usually assumed mechanism when PNS dysfunction reverses rapidly). With the exception of just 2 patients, we have not seen severe slowing of conduction, evidence of conduction block, or extreme prolongation of late response latencies—the abnormalities usually found in demyelinating neuropathies (McLeod *et al.*, 1973; Buchthal *et al.*, 1984). In 1 of these 2 patients, the association between her demyelinating neuropathy and Lyme borreliosis was quite tenuous. The other, reported in our initial series (Halperin *et al.*, 1987; Case 6), had a rather slowly progressive course, and was one of the oldest Lyme disease patients that we have evaluated. Whether other factors contributed to the severity of her neuropathy remains unclear. While the prolongation of terminal latencies which we have observed can be an early marker of a demyelinating disorder (McLeod *et al.*, 1973), it is difficult to imagine that all the patients presented here, who have generally had quite chronic and widespread symptoms, could have had a primarily demyelinating disorder which invariably affected only the distal axons, always sparing more proximal nerve trunks.

We have seen 2 patients with what initially appeared clinically to be AIDP. The first, who had the usual CSF and neurophysiological abnormalities of AIDP, is the more difficult to explain. She was in all ways typical of a postinfectious AIDP, and had nothing clinically to suggest Lyme borreliosis. Moreover, she responded very well to plasmaphoresis (without antibiotics). Our earlier experience with patients with Lyme arthritis has led us to conclude that immunosuppressive therapy is of limited benefit in this disorder, and may in fact be quite detrimental (Dattwyler *et al.*, 1988*a*). Therefore we suspect that this patient's case of AIDP was not causally related to her exposure to *B. burgdorferi* infection. The other patient's illness is more readily explained since his laboratory findings were completely inconsistent with AIDP. His neurophysiological abnormalities were indicative of distal axonal damage and polyradiculopathy, with no compelling evidence of demyelination. His CSF demonstrated a marked pleocytosis and he had anti-*B. burgdorferi* antibodies in both his serum and his CSF. It is interesting that the only other patient reported in the literature as having a demyelinating neuropathy associated with Lyme borreliosis (Sterman *et al.*, 1982) actually had findings very similar to those in this case. He too had a CSF pleocytosis and neurophysiological abnormalities comparable with this patient's. We suspect that that patient's neuropathy was similar to that in our patient and, in fact, was not primarily demyelinating. We conclude from these observations that primarily demyelinating neuropathies occur very rarely—if ever—in association with Lyme borreliosis.

The most common pattern of neurophysiological abnormality that we have observed has been the presence of a somewhat patchy axonal neuropathy, affecting distal axons most noticeably. The most commonly abnormal measures in these patients have been terminal motor latencies, sensory action potential amplitudes, and sensory CV, all of which reflect function of distal axons. Late response latencies have also tended to be abnormal, but to a lesser extent. Following antibiotic treatment, it is these same values which have improved the most consistently. Interestingly, these abnormalities are very similar to those reported in acrodermatitis chronica atrophicans (Hopf, 1975), a cutaneous manifestation of late *B. burgdorferi* infection reported much more frequently in Europe than in North America. Perhaps the fact that the patients we have seen—particularly those with painful radiculitis—have tended to have disease of somewhat longer duration than those with similar symptoms reported in the European literature, may explain why our findings resemble those found in European patients with more chronic infections. Our patients have also differed from those from Europe in that the latter typically have had painful radiculitis in a distribution corresponding to the site of the tick bite, while this has been less consistently observed in our population. Whether these disparities reflect true biological differences, or merely differences in case ascertainment or disease severity, remains to be determined.

Interestingly, most patients with typical 'painful radiculitis', and most with Bell's palsy, have had this same pattern of widespread abnormalities of nerve conduction, including abnormal sensory potentials, abnormalities that cannot be explained on the basis of a process simply affecting nerve roots. This suggests to us that all of these clinically rather different groups of patients may actually have very similar types of peripheral nerve involvement. This conclusion is further supported by published neuropathological studies in patients with European tick-borne, painful meningoradiculoneuritis (Camponovo and Meier, 1986; Vallat *et al.*, 1987)—as well as our own neurophysiological studies (Halperin *et al.*, 1987, and unpublished observations)—in which prominent abnormalities, including perivascular inflammatory infiltrates, have been seen in biopsied sural sensory nerves. In fact, the types of abnormalities, both neurophysiological and neuropathological, seen in painful radiculitis and in the milder, more diffuse neuropathy, are qualitatively quite similar, and we would suggest that these are merely different manifestations of similar pathogenic processes. This conclusion is also supported by an examination of the temporal course of these different syndromes. Although it was initially felt that the milder neuropathy was a manifestation of more chronic *B. burgdorferi* infection, in fact this syndrome occurs with essentially the same latency as does painful radiculoneuritis. The patients with milder syndromes merely took longer to seek medical attention.

In any patient who has noncompressive, nontraumatic abnormalities of single nerves or of small groups of nerves (such as a cranial mononeuropathy, patchy neuropathy or brachial plexopathy) the usual clinical assumption is that the underlying process is a form of multiple mononeuropathy, and that the most likely mechanism is vascular. The available neuropathological observations would support such a mechanism in many patients with Lyme-associated PNS involvement (Camponovo and Meier, 1986; Halperin *et al.*, 1987; Vallat *et al.*, 1987). Although there has been a report of cross-reactivity between anti-*B. burgdorferi* antibodies and peripheral nerve axons (Sigal and Tatum, 1988), it seems unlikely that such an antibody-mediated mechanism would account for the sort of patchy abnormalities that have been observed (particularly since morphological studies have failed to demonstrate antibody deposits in damaged nerves in any of these patients).

Our neurophysiological findings have generally been indicative of abnormalities of distal axons. A multiple mononeuropathy can mimic a distal axonopathy clinically, from the cumulative effect of multiple lesions along the course of nerves (Waxman *et al.*, 1976), so that the longest axons are the most likely to sustain damage. Recent work has suggested a similar pathogenic mechanism in the distal symmetric form of diabetic neuropathy, in which it appears that multifocal proximal vascular insults may summate to create the picture of a distal symmetric neuropathy (Dyck *et al.*, 1986*a*, *b*; Johnson *et al.*, 1986). Similarly, clinical and neurophysiological studies in patients with vasculitic neuropathies, particularly in those with more chronic, less fulminant forms, have demonstrated abnormalities similar to those that we have described, with relative preservation of motor CV, but frequent abnormalities of sensory conduction and terminal motor latencies (Peyronnard *et al.*, 1982; Kissel *et al.*, 1985). Perhaps in these patients a series of small vascular insults occurs along the course of a nerve, but these are too small to be locally apparent; only the cumulative effect would be evident distal to the sites of involvement, resulting in an apparent abnormality of the distal nerve terminals. One difficulty with this hypothesis is the relative rapidity with which our patients have improved after treatment; this would be difficult if the abnormalities were due to destructive lesions of proximal axons, and would suggest that any vascular insult would have to be incomplete, perhaps causing nerve hypoxia but not infarction.

At this point, we are unable to offer any definitive conclusions as to the mechanism of the neuropathies that we have observed. However, if, as we have suggested, most of the syndromes that occur are manifestations of a vasculopathy, this would greatly simplify the task of understanding how a single infectious disease could cause such a wide spectrum of peripheral nervous system abnormalities. Regardless of the pathogenic mechanism, however, four conclusions seem evident. (1) The PNS is very commonly involved in late Lyme borreliosis. (2) Despite the large number of different clinical syndromes that has been described, all share the property of being readily reversible with appropriate antibiotic therapy in almost all instances. (3) It is clear that neurophysiological testing is helpful in detecting peripheral nerve dysfunction in these patients, and offers a useful measure of disease severity in a disorder in which assessing disease activity is often very difficult. (4) Finally, and perhaps most importantly, it appears that despite the broad clinical spectrum of presenting manifestations, the neurophysiological abnormalities are surprisingly uniform, with strikingly similar findings in patients who clinically appear to have a mononeuropathy, a monoradiculopathy, or a disseminated polyneuropathy. This suggests to us that these vastly different clinical syndromes are merely different points on a continuum of PNS manifestations, all interrelated by a common pathogenic mechanism.

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DIFFUSE NOXIOUS INHIBITORY CONTROLS IN MAN

INVOLVEMENT OF THE SPINORETICULAR TRACT

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SUMMARY

In normal subjects, heterotopic painful stimuli induce simultaneous and parallel decreases in the sensation of pain and in the spinal nociceptive flexion (RIII) reflex evoked by electrical stimulation of the sural nerve. This inhibition of the RIII reflex is not seen in tetraplegic patients with clinically complete spinal cord transection, suggesting that supraspinal structures are involved in this type of inhibition, mediated through 'Diffuse Noxious Inhibitory Controls' (DNIC). In the present study, the effects of heterotopic nociceptive stimuli on the RIII reflex were examined in 3 patients with unilateral thalamic vascular lesions and in 3 with Wallenberg's syndrome (WS). In the former, as in normal subjects, nociceptive electrical conditioning stimuli applied to the analgesic hand produced a profound inhibition of the RIII reflex followed by long-lasting after-effects. No inhibition was observed in the WS patients. The same conditioning procedure applied to the nonanalgesic hand of the WS patients resulted in inhibition and after-effects similar to those observed in normal subjects. The fact that noxious but nonpainful stimuli triggered DNIC in the patients with thalamic lesions excludes the possibility that masking of pain by a second painful focus is mainly due to attentional processes. It is also concluded that lemniscal and spinothalamic pathways are not involved in the triggering of DNIC in man and it is suggested that the brainstem and probably the spinoreticular tract are key neuronal links in the loop subserving DNIC in man.

INTRODUCTION

It was reported previously that in normal human subjects painful stimuli applied to anatomically remote areas of the body strongly depress both a nociceptive flexion reflex in the lower limb (RIII reflex) and pain elicited by sural nerve stimulation at the ankle; it was also reported that nonnociceptive heterotopic stimuli were totally ineffective in this respect (Willer *et al.*, 1984). This suggested that the modulation of pain by such heterotopic nociceptive stimuli could be explained, at least in part, by a depression in the transmission of nociceptive signals at spinal level. On the basis of analogous animal studies (Le Bars *et al.*, 1979*a*, *b*; Le Bars and Villanueva, 1988), we proposed that such phenomena, which we termed Diffuse Noxious Inhibitory Controls (DNIC), might

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be mediated by a complex loop ascending from and descending to the spinal cord. The involvement of supraspinal structures in this loop was suggested by a subsequent study (Roby-Brami *et al.*, 1987) in which we compared the effects of heterotopic nociceptive stimuli on the RIII reflex in normal subjects with those oberved under similar conditions in tetraplegic patients suffering from clinically complete cervical spinal cord transections of traumatic origin. It was found that in normal subjects, the heterotopic nociceptive conditioning stimuli produced a profound depression, followed by long-lasting after-effects, of the RIII reflex elicited by sural nerve stimulation. By contrast, the same conditioning procedure did not produce any depressive effect on the similar nociceptive flexion reflex in tetraplegic patients. These data confirmed that supraspinal structures are involved in the loop responsible for triggering DNIC in man. The aim of the present study was to localize more accurately both the ascending path and the supraspinal level of these structures. For this purpose, we have compared the effects of heterotopic nociceptive stimuli on the RIII reflex in patients with unilateral thalamic vascular lesions with those observed in patients with unilateral lesions of the retro-olivary portion of the medulla (Wallenberg's syndrome).

METHODS

Patients

Three patients, each with a unilateral thalamic vascular lesion (TH) demonstrated by CT and 3 patients, each with a unilateral lesion of the retro-olivary portion of the medulla (Wallenberg's syndrome, WS), were investigated. The study was approved by a local ethics committee and the patients gave informed consent. They were selected on the basis of typical clinical features and CT data. In the TH patients, CT data permitted precise localization of the lesions and showed no evidence for the presence of any other lesions. The selection of typical WS cases was made on the basis of the clinical features which allowed the affected neural structures to be determined accurately (*see* references in Hommel *et al.*, 1988); in these patients, CT was used to confirm the absence of any other lesions. All patients had hemianalgesia contralateral to the lesion. In the WS patients, only thermal and pain sensation was diminished whereas in the TH patients, other cutaneous sensory modalities were also impaired. The main clinical features for both groups of patients are summarized in Tables 1 and 2.

Test procedure

During the experimental sessions, the patients sat comfortably and reclined in a specially designed armchair to ensure a state of general muscle relaxation. The method for eliciting and recording the nociceptive flexion RIII reflex has been detailed in a previous report (Willer *et al.*, 1984). Briefly, bipolar electrical test stimuli were applied to the sural nerve of the normal leg via a pair of surface electrodes (20 mm apart) placed over its submalleolar pathway. The stimulus consisted of a 20 ms duration volley of 5 rectangular pulses (1 ms duration), and was delivered once every 6 s from a constant-current stimulator. Electromyographic (EMG) responses were recorded from the ipsilateral biceps femoris muscle by means of surface electrodes fixed on the degreased skin overlying the muscle. The intensity of stimulation was adjusted to 20% above the RIII reflex threshold which gave rise to stable reflex responses with minimal fluctuations (Willer, 1985). Such a stimulus induced a slightly painful pin prick type of sensation which was well tolerated by all patients. Both the reflex responses and the stimulus intensity were continuously monitored on a storage oscilloscope during the experiments.

TABLE 1. MAIN CLINICAL AND RADIOLOGICAL FEATURES OBSERVED IN THE PATIENTS WITH THALAMIC LESIONS*

		Sensory loss				
Age (yrs)	*Sex*	*Thermal, pin prick*	*Light touch, proprioception*	*Motor disturbances*	*Visual disturbances*	*CT data*
37	M	L upper and lower limbs	L astereognosis	Transient L hemiparesis	None	R capsulo-thalamic haematoma
64	M	L hemibody	Decreased. L hemibody	L hemiparesis	None	R capsulo-thalamic infarction
52	M	L hemibody	Light touch decreased, normal proprioception	None	L hemianopia	R thalamic infarction, L capsular lacunar lesion

* These clinical data indicate that the thalamic terminations of the spinothalamic fibres were interrupted. The CT data show the thalamic location of the lesion and eliminate the existence of any other lesions except in the third case in which, although there was another lesion, it could not have interfered with the present results.

TABLE 2. MAIN CLINICAL FEATURES OBSERVED IN THE PATIENTS WITH WALLENBERG'S SYNDROME*

		Sensory loss				*Cranial nerve impairment*					
Age (yrs)	*Sex*	*Thermal pin prick*	*Light touch proprioception*	*Pyramidal signs*	*Cerebellar signs*	*V*	*VII*	*IX*	*X*	*XII*	*Hiccup*
65	F	L upper and lower limbs	Normal	None	R	R	R	R	R	0	0
69	M	R upper and lower limbs	Normal	None	L	L	L	L	L	0	0
71	M	R upper and lower limbs	Normal	None	L	L	L	L	L	0	0

* Patients were selected on the basis of the typical clinical features of the syndrome and on the lack of any other lesions (CT data). The clinico anatomical correlation based on the spectrum of these features was of lateral medullary infarction (Fisher *et al.*, 1961; Hauw *et al.*, 1976).

Conditioning procedure

The conditioning procedure was similar to that employed in a previous study (Roby-Brami *et al.*, 1987). Briefly, the nociceptive conditioning period consisted of electrical stimulation (1 ms duration pulses at 3 Hz) applied via 2 ring electrodes tied around the fourth and fifth fingers of the hand on the analgesic side for the TH patients (*see* Results) and successively on both sides for the WS patients (*see* Results). The intensity of stimulation was adjusted to the maximum tolerable (20–25 mA) when applied to the normal side. However, such stimuli were described as producing tactile and nonpainful vibrating sensations when applied on the analgesic side of either category (TH and WS) of patient. The test and conditioning stimuli were delivered in such a fashion that the recording of the RIII reflex was not invaded by any artefacts from the conditioning stimuli. After amplification, the EMG responses were digitized by an on-line computerized system. Each response was full-wave rectified and integrated between set points on the waveform which were chosen for each subject in accordance with the latency and duration of the RIII reflex; this was usually from 100 to 180 ms after the start of the test stimulus (Roby-Brami *et al.*, 1987).

General experimental procedure

At the beginning of the sessions, both the test and conditioning stimulus intensities were adjusted as described above. The test stimuli were then applied for at least 15 min with the conditioning stimuli delivered during the sixth and seventh minutes.

Analysis of results

For each subject, control responses were determined during the 2 min preceding the conditioning period. The mean control value was then calculated and each individual reflex response was expressed as a percentage of this mean. The mean of 10 successive responses was calculated for each minute of the experimental procedure.

RESULTS

Patients with thalamic lesions

In the 3 patients under study, the mean threshold for obtaining a nociceptive flexion reflex was 9.1 ± 0.6 mA. Increasing the current intensity to a slightly suprathreshold value (+20%) gave rise to a supraliminal RIII reflex (latency around 110 ms) which did not exhibit any noticeable change during the repeated application of the stimulus, as had been observed previously in normal and tetraplegic subjects (Roby-Brami *et al.*, 1987; Willer, 1989). As illustrated with a representative individual example in fig. 1, application of the heterotopic nociceptive conditioning stimuli on the analgesic side strongly depressed the RIII reflex. This depression occurred rapidly within the first minute with a dramatic total inhibition by the second minute of the conditioning period. The recovery was progressive but incomplete during the following 8 min of observation. Similar effects were observed for all 3 patients, with the RIII reflex being almost totally abolished during the second minute of the conditioning period. The overall effects are summarized in fig. 2. It is worth noting that the strongly nociceptive conditioning stimuli (21 ± 2 mA) when applied to the analgesic hand were never felt as painful but were described by the patients as producing a vibratory sensation. Since this procedure was found to induce a profound inhibition of the RIII reflex similar to that observed in normal subjects (Roby-Brami *et al.*, 1987) we judged it to be improper from an ethical standpoint to apply such nociceptive conditioning stimuli to the normal side of these patients.

Patients with Wallenberg's syndrome

In the 3 patients under study, the mean threshold for obtaining a nociceptive flexion reflex was 18.5 ± 5.7 mA from the analgesic side and 17.9 ± 6.2 mA from the other.

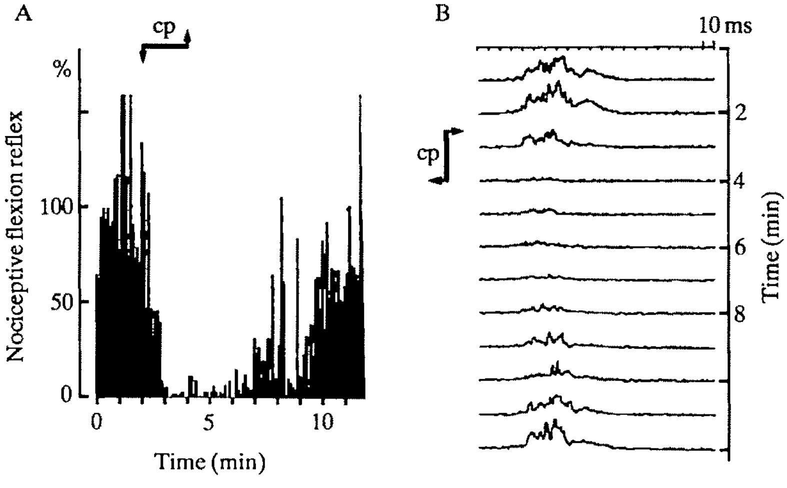

FIG. 1. Recordings from a patient with a thalamic lesion, showing inhibitory effects on one RIII reflex elicited by the nociceptive conditioning stimuli applied for 2 min to the analgesic hand. A, temporal evolution of single reflex responses. In the ordinate, individual responses are expressed as percentages with references to the mean value observed during the 2 min control period; cp = conditioning period. B, each trace is an average of 10 full-wave rectified successive reflex responses; the temporal evolution is seen from top to bottom. Note in both A and B, the prominent inhibition of the RIII reflex during and following the conditioning period.

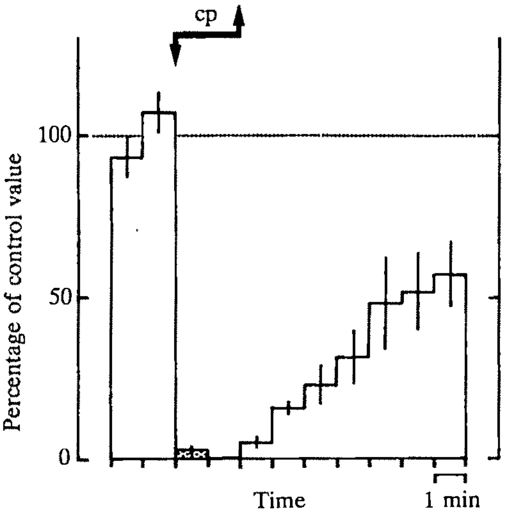

FIG. 2. Recordings from the 3 patients with thalamic lesions showing overall inhibitory effects on the RIII reflex. Each column represents the mean value ± SEM for 10 successive reflex responses expressed, in each individual case, as a percentage of the control values. Note the very strong inhibition during the conditioning period (cp, arrowed) and the long-lasting after-effects which outlast the 7 min period of post-cp observation.

As with the TH patients, a slightly suprathreshold stimulus intensity (+20%) gave rise to a supraliminal RIII reflex (latency around 110 ms) which did not exhibit significant changes during the repeated application of the stimuli to the sural nerve. As illustrated with a representative example in fig. 3A, application of the heterotopic nociceptive conditioning stimuli to the fingers on the analgesic side clearly induced an increase in

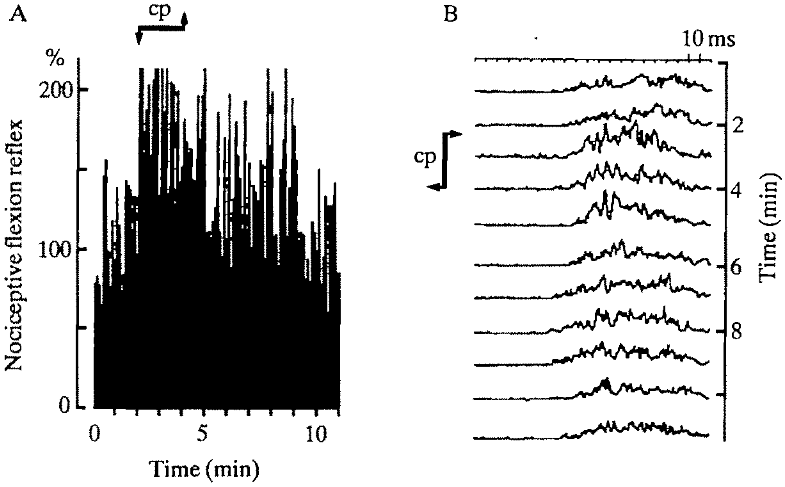

FIG. 3. Recordings from patient with Wallenberg's syndrome showing effects on the RIII reflex elicited by the nociceptive conditioning stimuli applied for 2 min to the analgesic hand (presentation as in fig. 1). Note the lack of any inhibitory effect. The RIII reflex was, in fact, slightly increased during the conditioning stimulation period.

the RIII reflex. This facilitatory effect occurred rapidly and reached a maximum within the first minute of the conditioning procedure; thereafter it decreased progressively but partially recovered during the following 7 min period of observation. By contrast, application of the nociceptive conditioning stimuli to the fingers of the normal hand strongly depressed the RIII reflex in a similar way to that observed in TH patients and normal subjects (fig. 3B). Similar effects were observed in all 3 patients, including a

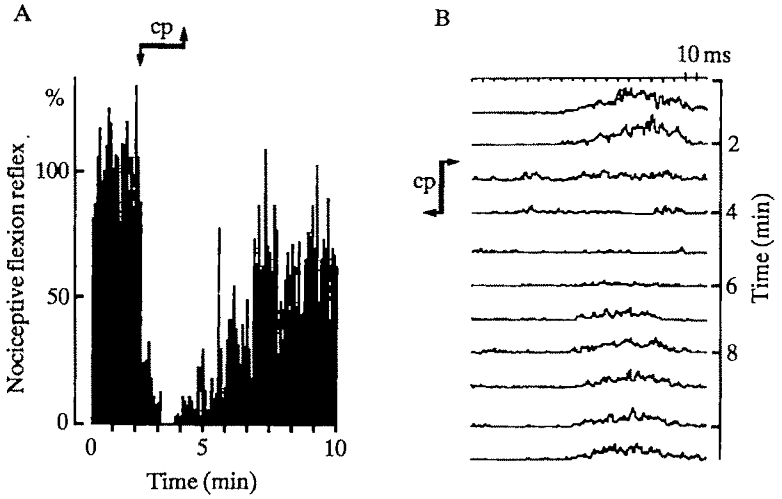

FIG. 4. Recordings from patient with Wallenberg's syndrome (same patient as in fig. 3) showing inhibitory effects on the RIII reflex elicited by the nociceptive conditioning stimuli applied for 2 min to the 'normal' hand (presentation as in fig. 1). Note the prominent inhibition observed during and following the conditioning period.

more or less pronounced facilitation of the RIII reflex when the analgesic side was stimulated (fig. 4A) and clear-cut inhibitory effects when the other side was stimulated (fig. 4B). As with the TH patients, it should be mentioned that the strongly nociceptive conditioning stimuli (24 ± 4 mA) applied to the analgesic hand were never felt as painful but were reported as producing tactile vibrating sensations. By contrast, when the other side was stimulated, the conditioning nociceptive stimuli were reported to produce pricking and burning sensations of pain which persisted between the stimuli and disappeared progressively in 20–30 s after the end of the 2 min conditioning period.

DISCUSSION

The present study shows that in patients with thalamic lesions (TH patients), a nociceptive electrical conditioning stimulus applied to the analgesic hand produces a profound inhibition followed by long-lasting after-effects on a lower limb nociceptive flexion reflex elicited by sural nerve stimulation. These results are similar to those observed previously in normal subjects (Roby-Brami *et al.*, 1987). By contrast, in patients with typical Wallenberg's syndrome (WS patients), the same conditioning procedure, namely nociceptive electrical stimuli applied to the analgesic hand, did not produce any depressive effect on the lower limb flexion reflex. This result is similar to that observed previously in patients with a total spinal cord transection of traumatic origin (Roby-Brami *et al.*, 1987). However, the same conditioning procedure applied to the nonanalgesic hand of the WS patients resulted in inhibitory effects and after-effects similar to those observed in normal subjects and TH patients.

The effects observed in both types of patients were so clear that we did not judge it to be necessary to extend the study to a larger number of patients. However, there are three minor findings in the study which appear to need further investigation. (1) The threshold of the RIII reflex in TH patients (9.1 ± 0.6 mA) was very similar to that in normal subjects (Willer *et al.*, 1984), whereas that found in WS patients was much higher (18.5 ± 5.7 mA). (2) The inhibitory effects and after-effects of the conditioning stimuli seemed to be more pronounced in TH patients than in normal subjects or in WS patients when, in the last of these groups, the conditioning stimuli were applied to the nonanalgesic hand (compare figs. 2 and 5B). (3) In WS patients, a slight, albeit nonsignificant (paired t test), facilitation of the RIII reflex was observed when the conditioning stimuli were applied to the analgesic hand (*see* fig. 5A); a similar observation was made previously in tetraplegic patients (Roby-Brami *et al.*, 1987). At the present time, we do not have any satisfactory explanation for these three findings which, in any case, require confirmation with a larger number of observations. The finding that the threshold of the RIII reflex evoked from both sides in WS patients was twice that found in normal subjects implies that more afferent fibres should be activated to evoke the reflex in these patients. This was also the case when the heterotopic conditioning stimulation was applied. However, we do not think that this fact could introduce a bias in our present results since clear-cut opposite effects were elicited from either side.

We will now consider the electrophysiological data and the clinicoanatomical features

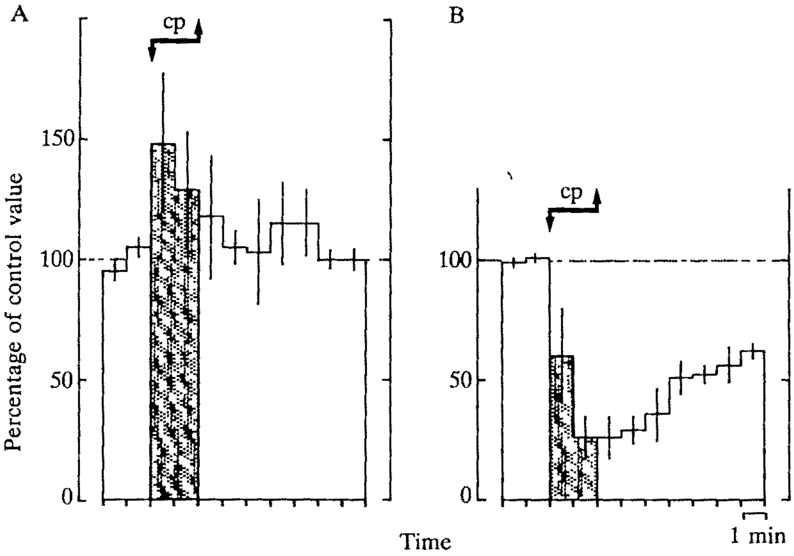

FIG. 5. Recordings from patients with Wallenberg's syndrome showing overall effects on the RIII reflex recorded when the conditioning stimuli (cp) were applied to the analgesic hand (A) or to the normally sensitive side (B) (presentation as in fig. 2).

for each group of patients in an attempt to determine which ascending pathway(s) and supraspinal structures are responsible for triggering the inhibitory effects induced by heterotopic nociceptive conditioning stimuli (Diffuse Noxious Inhibitory Controls, DNIC) in normal subjects. Based both on clinical and CT data, it was clear that the first group of patients (TH) showed unilateral thalamic or capsulothalamic vascular lesions and had no other demonstrable lesions. This indicates that the lesion involved neurons of the lateral thalamus and the impinging terminals of both the lemniscal and the spinothalamic tracts. In these patients, a profound inhibition of the RIII reflex could be triggered by nociceptive stimulation of the analgesic hand. It is not surprising that a lesion of the lemniscal pathway did not alter DNIC since nonnociceptive stimuli which produce specifically tactile sensations, do not modify the RIII reflex when applied to heterotopic areas in normal subjects (Willer *et al.*, 1984; Roby-Brami *et al.*, 1987). In addition, it has been shown previously that the degree of inhibition of the RIII reflex induced by heterotopic noxious thermal stimulation parallels both the severity of pain and the response of peripheral nociceptors elicited by the conditioning stimulus (Willer *et al.*, 1984). The ascending fibres involved in the triggering of DNIC in man would seem therefore to be those, or some of those implicated in nociception. In this respect it is also possible to exclude, on the basis of the present data, any involvement in the DNIC mechanisms of the postsynaptic fibres running in the dorsal columns. Although there is a wealth of classical clinical data in man (Brown-Séquard syndrome, syringomyelia, tabes dorsalis) which clearly indicated that no sensation of pain can normally be evoked by signals in the dorsal column pathways (Adams and Victor, 1985), their role in pain has been suggested on the basis of animal data (*see* references in Besson and Chaouch, 1987).

Finally, and more importantly, our results in TH patients allow the exclusion of spinothalamic fibres in the afferent pathways which mediate DNIC since their destruction at the thalamic level did not prevent the inhibitory effects of the nociceptive conditioning stimuli. The role of the spinothalamic tract in the perception of pain is well established in both man and animals (Mehler *et al.*, 1960; Kerr and Lippman, 1974; Willis and Coggeshall, 1978; Willis, 1984; Albe-Fessard *et al.*, 1985; Besson and Chaouch, 1987). Accordingly, the strongly nociceptive conditioning stimuli applied to the analgesic hand of the TH patients was never reported to be painful but was described as producing tactile and vibrating sensations. Our present data are in accordance with those of Villanueva *et al.* (1986*a*), who investigated the ascending pathways involved in the triggering of DNIC in the rat. These authors observed that section of the dorsal columns or lesioning of the ventrobasal thalamic complex did not modify the effects of DNIC on trigeminal convergent neurons, thus ruling out the participation of both the lemniscal pathways and the spinothalamic tract in these processes.

As a nociceptive but nonpainful stimulus-triggered DNIC in the TH patients, it is unlikely that the inhibition of the RIII reflex and the simultaneous sensation of pain in normal subjects are due mainly to attentional processes elicited by the painful component of the conditioning stimuli. We reached an identical conclusion on the basis of observations made during an investigation using the same procedure on a patient with a parietal lesion and applying the nociceptive conditioning stimuli to the analgesic side (unpublished data). We are emphasizing these points as attentional factors do influence pain perception (Willer *et al.*, 1979; Bushnell *et al.*, 1985) and it is often believed that the 'masking' of pain by a second, distant painful stimulus can be explained by competition between the foci of attention. Our present results show that the spinal transmission of nociceptive signals is clearly impaired by heterotopic noxious stimuli in the absence of any changes in attentional processes due to pain. It can confidently be inferred that identical mechanisms are brought into play in normal subjects.

The WS patients were selected on the basis of typical clinical characteristics and the fact that CT did not reveal any other lesions in the brain or spinal cord. Thus the present data provide clear evidence that propriospinal neurons are not involved in the DNIC circuitry, a possibility that could not be totally excluded in the previous study performed in tetraplegic patients (Roby-Brami *et al.*, 1987). Since our patients exhibited typical Wallenberg's syndrome, it was possible to determine with accuracy the lesioned structure in the medulla using classical clinicoanatomical correlations (Currier *et al.*, 1961; Fisher *et al.*, 1961; Hauw *et al.*, 1976; Hommel *et al.*, 1988). Our present data clearly shows that the lesion of some medullary structure(s) and/or of ascending fibres of the retro-olivary portion of the medulla is/are of prime importance for triggering DNIC in man. Since DNIC are specifically triggered by nociceptive events, we will consider the medullary regions which reasonably could be involved in these processes. In typical examples of Wallenberg's syndrome, it is known that the ischaemic lesion includes fibres of the lateral spinothalamic tract. Both spinothalamic and spinoreticular fibres run in this tract; the latter terminate largely in the caudal and lateral portions of the medullary reticular formation (Mehler *et al.*, 1960; Bowsher, 1962; Brodal, 1981; Carpenter and Sutin, 1983). Since the spinothalamic fibres are not involved in the triggering of DNIC (*see* above) it can be suggested that the remaining fibres running in the lateral spinothalamic tract, namely the spinoreticular fibres, convey most of the nociceptive information that triggers DNIC. However, in typical WS patients who do not show evidence of corticospinal tract involvement, hiccup or twelfth nerve and lemniscal impairment, the ischaemic lesion is limited to the lateral part of the medulla (Fisher *et al.*, 1961; Hauw *et al.*, 1976; Carpenter and Sutin, 1983) and does not reach the ventromedial part of the medulla where the majority of spinoreticular afferents terminate (Bowsher, 1957, 1962, 1976). It must therefore be concluded that the lack of triggering of DNIC which we observed when the conditioning procedure was applied to the analgesic hand of WS patients was mainly due to the lesioning of spinoreticular fibres before they reached their targets.

Thus it appears to be unambiguous from the present study that the brainstem is the site of a key neuronal link in the loop subserving DNIC in man. From a neurological standpoint, our data can be considered as the first functional evidence for the existence of a spinoreticular system involved in pain modulation in man. Indeed, while there is much neurological evidence for the role of the spinothalamic tract in pain processes (Adams and Victor, 1985; Besson and Chaouch, 1987), the proposed role of the spinoreticular tract in man is based mainly on anatomical observations (Bowsher, 1957, 1962, 1976; Mehler *et al.*, 1960; Brodal, 1981). These studies have shown that the majority of spinal afferents ascending in the anterolateral quadrant of the cord terminate in the ventromedial part of the brainstem reticular formation. We have demonstrated that the blockade of spinoreticular but not of spinothalamic pathways blocked a nociceptor-evoked event. This again emphasizes the fact that the anterolateral quadrant cannot be regarded as being formed only by the spinothalamic tract, as is frequently believed so far as pain is concerned. The present data are in keeping with work performed in the rat in which it was found that the ascending pathways involved in the triggering of DNIC were restricted to the anterolateral quadrant and most probably involved spinoreticular fibres (Villanueva *et al.*, 1986*a*). Interestingly, in the rat, although the signals responsible for triggering DNIC were mainly crossed, there was a significant uncrossed component. In the present study, all the spinoreticular fibres involved in the triggering of DNIC seemed to be crossed without the participation of any uncrossed component. However, such an uncrossed component could have been masked by our experimental conditions in which the thresholds of the RIII reflex and hence the test stimuli, were significantly increased in the WS patients. This seems very likely in view of the substantial number of anatomical studies which have shown that the spinoreticular tract has bilateral projections in man; in particular, it has been shown that a unilateral lesion of the anterolateral quadrant results in bilateral degeneration of spinoreticular fibres (Bowsher, 1962). In any case, from the evidence in the rat, the crossed component of the spinoreticular fibres which are involved in triggering DNIC, appears very much to be the dominant one.

In summary, the present study strongly suggests that DNIC circuitry, involving the brainstem, exists in man. The crossed component of the spinoreticular pathways seems to be of prime importance in this system. This circuitry is probably similar to that described in the rat where it was found that the signals responsible for DNIC are transmitted with the ventrolateral quadrant and the dorsolateral funiculus containing the ascending and descending pathways respectively (Villanueva *et al.*, 1986*a*, *b*). We therefore believe that the clinical and electrophysiological investigations of both spinoreticular and descending inhibitory pathways modulating the spinal transmission of nociceptive information would be possible in humans, using the procedure described herein. Such investigations could be of great interest in patients suffering from various neurological disorders which may affect these pathways.

ACKNOWLEDGEMENTS

We wish to thank Miss J. Chandellier for technical assistance and Dr S. W. Cadden for correcting the English. This work was supported by l'Institut National de la Santé et de la Recherche Medicale (INSERM), CRE No. 886019 and by la Fondation pour la Recherche Medicale (FRM).

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Brain (1990), **113**, 1235–1248

BOOK REVIEWS

Advances in Contemporary Neurology. Edited by Fred Plum. 1988. Pp. 211. Philadelphia: F. A. Davis. Price £29.12.

This book is the twenty-ninth volume in the distinguished 'Contemporary Neurology Series', edited by Professor F. Plum, which has contained a number of modern neurological classics. It was therefore rather a surprise to find that this volume is only a compilation of six essays, and led me to consider whether this particular series had run out of steam. However, on reading through these essays it is apparent that, as always, Professor Plum has chosen the topics carefully and this volume certainly maintains the fine tradition of the series. The essays are topical, well written and most of them are of considerable interest to the practising clinical neurologist.

The first chapter on the neurological complications of AIDS is the best summary of this topic I have read. The background virology and immunology is particularly clearly written, and the clinical and pathological aspects are very comprehensive. Of similar clarity and thoroughness is the chapter on mitochondrial myopathies and encephalopathies which are of increasing importance when considering the 'unusual' neurological patient.

The so-called post-polio syndrome has become an important clinical topic, particularly in the United States, and the chapter on this subject provides a well-balanced view. The other mainly clinical topic is on tuberculosis of the central nervous system and here Professor Plum should perhaps have spread the authorship of the volume a little more beyond the confines of New York. Although this chapter is well written and illustrated, it is largely based on 13 case reports of meningeal and parenchymal infection seen over more than a decade in one hospital. Many physicians in other hospitals around the world see this number in less than a year and may have offered somewhat different approaches to management.

The remaining two chapters are on the selection of anxiolytics in clinical neurology and on prefrontal-limbic systems. The former is of limited interest to most neurologists, particularly as the use of benzodiazepines is rapidly diminishing, at least in the United Kingdom. The subspeciality of behavioural neurology is advancing rapidly and the final chapter on prefrontal-limbic systems is an excellent and clear review of this difficult topic.

The price of the book is very reasonable and there is plenty to interest most clinical neurologists. I would therefore thoroughly recommend this new addition to the Contemporary Neurology Series.

Christopher Kennard

Disorders of Voluntary Muscle. Edited by Sir John Walton. Fifth edition. 1988. Pp. 1166. Edinburgh: Churchill Livingstone. Price £95.00.

Ever since the first edition of this book was published in 1964, it has remained a standard reference for scientifically based clinical neuromuscular neurology (with a substantial emphasis on myology) around the world. With each subsequent edition, the book has lived up to its original high calibre and kept up with new developments in the rapidly evolving field of neuromuscular diseases. The fifth edition has been substantially reorganized, with the addition of several valuable new chapters, including immunology, pathophysiology of excitation in skeletal muscle, cell biology, parasitic diseases, orthopaedic management, drug-induced neuromuscular diseases, and myotonic disorders. Despite this expansion, the number of pages was kept to practically the same as in the previous edition by prudent condensation of other chapters without creating important gaps.

The momentous developments in molecular biology during the past 4 years have created a large body of revolutionary new knowledge in several neuromuscular diseases, such as Duchenne/Becker dystrophy, malignant hyperthermia and myotonic dystrophy. Further developments are, no doubt, on the horizon, including advances in therapeutics. This will necessitate an updated edition of the volume much sooner than the interval of 7 years between the last two editions (1981 and 1988), if the book is to maintain a leading role in the field.

The fifth edition of *Disorders of Voluntary Muscle* will be found very useful and cost-effective by clinical neurologists and neuroscientists, internists, orthopaedists, rheumatologists, electromyographers, physiatrists and students in these disciplines. It certainly belongs to the shelves of every major medical library.

GEORGE KARPATI

James Parkinson: His Life and Times. By A. D. Morris. *History of Neuroscience*. Edited by F. Clifford Rose. 1989. Pp. 208. Boston and Basel: Birkhäuser. Price SFr 98.00.

James Parkinson's life was passed in an age full of interest for social and political historians, and students of art, literature and architecture, as well as of medicine. As a young man, Parkinson would have followed the American Revolution, the French Revolution, and then the long war with France and Napoleon. His life coincided with the steam engine of James Watt, and the pottery of Josiah Wedgewood. James Parkinson is remembered today for *An Essay on the Shaking Palsy*, written in 1817 at the age of 62, and later canonized by Charcot in the term 'la Maladie de Parkinson'. This syndrome so brilliantly described by Parkinson attracted some of the best minds of nineteenth century medicine and neurology, who described many details of its course and incidence, and speculated about its treatment and neuropathology. A further understanding of the genesis and control of this saddest of diseases had to wait until the present century. However, in his own time, Parkinson was better known as an energetic surgeon, apothecary and man-midwife to the poor of the Parish of St Leonard, and medical attendant of the madhouse of Holly House, Hoxton, as well as a political radical who sought universal suffrage, parliamentary reform, and the foundation of democracy in Great Britain. All his life testifies to frankness, sincerity and integrity in everything he did. In the absence of a portrait of Parkinson we must look to his friend, Dr Gideon Algernon Mantell, army surgeon of Lewes, and a celebrated geologist, who gave the only description of his appearance and personality. 'Mr Parkinson', wrote Mantell, 'was rather below middle stature, with an energetic intellect and pleasing expression of countenance, and of mild and courteous manners, readily imparting information either on his favourite science or on professional subjects.' One suspects that Parkinson would have achieved great distinction in any profession or different political climate. His characteristics were very similar to those of the Quaker savant of Philadelphia, Benjamin Franklin, and both men were intrigued by the effect of lightning. Both men were prolific authors, with a total of over 40 medical treatises, tracts and pamphlets, admonitions to the young, and elegant folios about geology attributed to Parkinson. In his 548-page *Medical Admonitions*, Parkinson's Table of Symptoms extends from 'anxiety and appetite (loss of)' to 'wakefulness, weakness, and yawning'. He was vitally concerned with then available treatments, many of which did not escape his fierce criticism; 'Dr James' Powder and Emetic Tartar' were much advertized nostrums which Parkinson attacked as being so violent as to require the utmost caution in administering them. His *Chemical Pocket Book* went through many editions in England and America, and must have sold well. He described in published case reports trismus, hydrophobia, fever, rupture and gout, which, like his father he suffered from himself. He wrote political tracts under the pseudonym 'Old Hubert'. These included *An Account of some Peculiar Manners and Customs of the People of Bull-land, or the Island of Contradictions* (1795), as well as *Pearls Cast Before Swine* (1793) and *Revolution without Bloodshed—or Reformation Preferable to Revolt* (1794). His notoriety here gained him the honourable titles of Republican, Democrat and Leveller. As a Sunday School Superintendent, his most useful work may have been *Dangerous Sports* (1808), a series of stories for children, warning against the playing of dangerous games. His concern for the young as well as old was shown by his post as Innoculator at the premises of the Hoxton Academy Chapel Sunday School. However, his main claim to authorship during his lifetime came not from his treatise on Parkinson's disease, other medical or political writings, but from palaeontology, and his publication of three elegant quarto volumes, *Organic Remains of a Former World*. This was a practical treatise on fossils, many gleaned by Parkinson himself on outings to the clay and gravel pits of Shoreditch and Hackney.

This marvellous account of a full and useful life is a worthy memorial to the scholarship of the late A. D. Morris. Morris was Medical Superintendent of St Leonard's and St Matthew's Hospitals in Shoreditch from 1945 to 1955, and during this time he gained an extraordinary knowledge of the east end of London and its inhabitants. His interest in Parkinson dated from this period, and he had contact with Parkinson's descendants, including his greatgranddaughter, Miss Florence Brown, then aged 95. The papers left at his desk included a detailed biography of James Parkinson, who comes to life in every page of this first full-length and definitive account. The book is well edited and produced, with an outstanding bibliography and reprint of the *Essay on the Shaking Palsy*, alas not in facsimile. The book gives a unique insight into medicine at the start of the nineteenth century, and the life of a most extraordinary and good man.

DAVID PARKES

Clinical Trial Methodology in Stroke. Edited by Willem K. Amery, Marie-Germaine Bousser and Frank Clifford-Rose. 1989. Pp. 286. London: Bailliere Tindall. Price £23.00.

Stroke is the commonest structural disease of the brain and is the third largest cause of death and second largest cause of chronic disability in developed countries. It is not surprising, therefore, that constant efforts are made to find a 'cure', none of which has met with success. The failure may in part be due to the way in which people have gone about the task. It is for this reason that a group met at the Corsendonk Priory in Belgium hoping, no doubt, to be inspired by the spirit of Erasmus who wrote his Laus Stultitiae there.

They covered a large field discussing, among other things, prognostic factors, methods of patient assessment in both the acute and chronic stage, and trial methodology in strokes, subarachnoid haemorrhage and carotid endarterctomy. Papers were presented with very full bibliographies followed by discussion, which has been skilfully edited. Few conclusions were reached though this was not the fault of the participants but rather because of the present state of knowledge. The participants did, however, miss an opportunity to come to grips with the future of clinical trials in the field of strokes. So many trials have been done and, whilst many were of poor quality, others were of good standard yet we are no nearer knowing how to treat strokes. Mention was made of the need for stratification by pathophysiology and by the therapeutic time window but these themes were not developed as they should have been. There is still too much concern with trial methodology, which is admittedly important, at the expense of asking the right questions in relation to narrowly defined pathophysiological categories. Lack of precision in this area cannot be compensated for by bumping up the numbers in a trial.

Despite this the book makes a valuable contribution by pointing out all the mistakes that have been made and the pitfalls to be avoided. It should not only be read but studied in depth by anyone thinking of undertaking a clinical trial in the field of stroke.

JOHN MARSHALL

Alzheimer's Disease: Towards an Understanding of the Aetiology and Pathogenesis. *Current Problems in Neurology 11*. Edited by D. C. Davies. 1989. Pp. 136. London: John Libbey.

The discovery in 1981 of shrinkage or loss of nucleus basalis cells with their cholinergic projections focused particular interest in the role of the subcortex in Alzheimer's disease. Disruption of the cholinergic system in experimental animals interferes with learning and memory but, as is pointed out by contributors to this short monograph, in Alzheimer's disease some other neurotransmitters are affected and pathology is not restricted to the subcortex. It is the connections of affected neurons which determine disease susceptibility, not the transmitter. Thus in Alzheimer's disease, nigral neurons are unchanged but adjacent dopaminergic cells with projections to the cortex are affected. The temporal lobe is severely damaged with extensive changes in the hippocampal formation and entorhinal cortex but, strangely, less so in the motor cortex. In this book, the significance of the pathology of the neocortex and limbic structures in dementia in comparison with the subcortex is an important theme—indeed, Alzheimer's disease has long been recognized to predominantly affect the cerebral cortex. Thus within the temporal cortex only about half the normal number of large pyramidal cells are found. Typical neuropathological features are found in the hippocampal formation with loss of pyramidal and stellate neurons leading to disconnection of the hippocampus which could alone well account for the typical memory deficits. There is increasing evidence that the disease process may spread along cortical connecting fibres, possibly via the olfactory system since pathological changes are seen in nasal epithelial tissue (Talamo *et al.* (1989), *Nature*, 337, 736–739). As to the pathogenesis, it is argued that neuritic plaques mark the site of the primary lesion and that neurofibrillary tangles occur as a generalized response to damage to nerve terminals, possibly through environmental factors such as aluminium and silicon. The isolation and sequence of an amyloid plague A4 peptide with homology to cerebrovascular amyloid suggests a haematogenous origin of the polypeptide. The controversial suggestion that neurofibrillary tangles are also composed of A4 peptide and the immunochemistry of the cytoskeletal elements are discussed (Chapters 5 and 6). Unfortunately, the earlier excitement following the identification of the familial Alzheimer's disease locus on chromosome 21 has not been followed by the finding of a similar site for the amyloid precursor gene in sporadic cases (Chapter 10).

The various contributors to this book have all written readable and thoughtful accounts of the subject, covering advances up to about 1988. Although only a brief index is provided, the overall standard of this reasonably-priced monograph is good.

A. N. DAVISON

Manuel de Neuropathologie. Third edition. By J. Poirier, F. Gray and R. Escourolle. 1989. Pp. 267. Paris: Masson. FFr 350.00..

Here is the third edition of the classic 'Manuel' whose second edition by Raymond Escourolle and Jacques Poirier was translated into English as the *Manual of Basic Neuropathology* by the late Lucien Rubinstein. That second edition was also translated into Spanish and Dutch which is in itself a proof of its wide success around the medical world. Raymond Escourolle, who was the distinguished Head of the Charles Foix Laboratory in 'La Salpêtrière', died in 1984 and Jacques Poirier asked Françoise Gray to collaborate on this third issue, as well as Jean-Jacques Hauw and Romain Gherardi. The result is a new 'tour de force', the whole field of neuropathology being very clearly exposed in 267 pages, 282 figures and drawings. All the figures are of excellent quality and the drawings are very explicit. After a clear analysis of the basic lesions which can involve the central nervous system, each chapter is well presented.

These past 10 years have been marked by much progress in our speciality and all these advances are included or mentioned in this 'manuel'. The pathology of AIDS is described at length, as well as certain features of cerebral amyloid angiopathy. The sections on muscle and peripheral nerve pathology have been almost entirely rewritten by Romain Gherardi, with the emergence of new entities such as peripheral neuropathies associated with an IgM monoclonal gammopathy and the POEMS syndrome. Adult polyglucosan body disease and the cerebral manifestations of Whipple's disease are described and very well illustrated. Adrenoleucodystrophy, the other leucodystrophies and the ceroid-lipofuscinoses have been reclassified. Each chapter is clearly written for students or beginners in this particular field of pathology, whether they come from the fields of neurology, neurosurgery or pathology. The book will also be very useful for experienced pathologists who are not used to dealing with the difficulties of neuropathological material. This third edition fulfils these functions admirably. The references are restricted to 30 books devoted to general neuropathology or to some of its particular fields.

The style is precise and clear ... for those who read French. But an English edition by the late Lucien Rubinstein is in press and will be available in a few months. Anyway, this French edition deserves a success as great as its two predecessors.

CLAUDE VITAL

Treatment of Glioma. Edited by Jiro Suzuki. 1988. Pp. 245. Berlin: Springer. Price DM 148.00.

This is a monograph largely devoted to original, and often previously unpublished, observations, both scientific and clinical, on the use of a nitrosourea, ACNU, which has been developed recently in Japan, alone or in combination in the treatment of glioma. Professor Suzuki has written an introduction and edited a volume in which a large majority of the 16 contributors are from his department in Sendai.

The book is divided into 3 sections, the first dealing with statistical aspects of natural history of these tumours, the second with basic laboratory studies relevant to optimizing the use of the drug ACNU and the third describing clinical studies in which the drug has been applied in different kinds of malignant brain tumour. The first chapter of the statistical analysis section describes the epidemiology and natural history of malignant primary brain tumours in north-east Japan in the 5 year period 1980 – 1984 based on 481 histologically verified cases in a total series of 660. The second chapter is an excellent review of the existing literature on the treatment of malignant glioma, reviewing specifically reports of results in 265 series of patients with glioblastoma and concentrating principally on an analysis of 48 reports of this kind where survival has been ascertained. The longest chapter in the book, amounting almost to one-third of its complete length, is in the section concerning basic laboratory studies and describes scientific experiments on cultured glioma cells elucidating the interaction between effects of radiation, ACNU and another drug, 5-fluorouracil. In this section further chapters are devoted to pharmacokinetics of ACNU studied by levels in blood, CSF and tumour samples of patients treated with the drug, as well as a study of oxygenation of glioma cells in situ by direct measurement. The latter is in fact an original scientific paper which describes the measurement of the oxygen pressure in brain tumour tissue and in surrounding normal brain, and one hopes that it will reach more general publication in a scientific journal. The final clinical section contains 9 original papers with much data which is previously unpublished. A novel form of treatment using radiation together with ACNU and a 5-fluorouracil precursor is described in detail and the results of using this in high grade gliomas, as well as in low grade tumours, oligodendrogliomas, ependyomomas and medulloblastomas are described. The results in grade 111 gliomas appear to be good but are much less satisfactory in glioblastoma. It is more difficult to reach definite conclusions about the results in the other tumours where the numbers treated are smaller.

The book is very well produced with clear tables and graphs.

This monograph will be of great interest to specialists concerned with the management of glioma and other primary malignant brain tumours. It introduces much previously unpublished data as well as reviewing the relevant existing literature. To the specialist reader it is particularly encouraging to see the attempt to optimize treatment strategies for glioma by experimental methods in vitro and then to proceed to attempt to improve clinical management on the basis of this rationale.

D. G. T. THOMAS

Vision and the Brain: The Organisation of the Central Visual System. Edited by B. Cohen and I. Bodis Wollner. 1989. Pp. 400. New York: Raven Press. Price $156.50.

This book originates from a meeting held in New York at the end of 1987 under the auspices of the Association for Research in Nervous and Mental Disease. The purpose of the meeting was to review recent work illustrating the separate functioning of the various parts of the visual system and relate this, where possible, to clinical neuro-ophthalmology.

When picking up yet another volume of conference proceedings I usually experience a slight decline in spirits. My enjoyment of just a few interesting papers is usually countered by my annoyance at the frequent reports which should have been submitted to refereed journals before being allowed the light of day. Alternatively many of the reports have already been published and do not deserve another airing. By the time the end of the book has been reached my usual conclusion is that the only people likely to benefit by the whole process are the shareholders of the publishers.

A quick look down the list of contents in this volume, however, immediately raised my spirits. This is definitely not the usual set of conference proceedings. Rather, it is a carefully constructed volume containing reviews of many of the existing areas of current research interest in visual function. The emphasis is on how the visual system has evolved as a complex set of subsystems, each with their own specific function, but all being intertwined to provide the final visual percept. For example, there are the parvocellular and magnocellular visual pathways, or separate extrastriate cortical visual areas such as V4 and V5, each predominantly concerned with colour and motion, respectively.

On the motor side saccadic and smooth pursuit eye movements are controlled by separate neural subsystems, but as with the visual pathways intricate connections exist between them.

The volume contains sections on retinal and geniculate organization; central processing, development and amblyopia; studies on central visual system organization; the visual-oculomotor interface; new techniques for study of the visual system and, finally, central visual system pathology, particularly Parkinson's disease, multiple sclerosis and Alzheimer's disease.

The chapters offer, on the whole, clear concise reviews which summarize a body of work usually emanating from each author's laboratory. There is much to interest both the visual scientist and clinician who wish to update themselves on the latest developments both at a basic and clinical level. It is perhaps rather invidious to pick out specific examples from the 18 chapters. I would certainly recommend the chapter by Livingstone on central visual processing and the segregation of form, colour, movement and depth processing. Here you can learn about many of the tricks of the visual system, a number of which, as it turns out, are intuitively used by painters and designers.

A number of the chapters on retinal, geniculate and cortical visual function concentrate on the neurotransmitters. This is an area of great interest, rapidly moving us on from the strictly single cell electrophysiological approach used so successfully by Hubel and Wiesel. It is by studying the neuropharmacology of the visual system that we are most likely to determine potential therapies for a variety of different disorders, particularly of a developmental type such as amblyopia and strabismus.

Three chapters deal with new techniques with which to study the visual system; pattern electroretinography, positron emission tomography (PET) and magnetoencephalography (MEG). Although functional activation of the striate and extrastriate visual cortices using PET is only just beginning, its ability to determine the relationship between physiology and anatomy as reviewed by Raichle will undoubtedly lead to great advances in our understanding of both normal and abnormal visual function in man. Although very much in its infancy, the technique of MEG also has great potential, particularly as it is completely noninvasive. The chapter by Kaufman and Williamson, pioneers in this field, rapidly moves the reader on from the technology of the SQUID (Superconducting Quantum Interference Device) to its application in locating specific modes of neuronal activity in the striate and extrastriate visual cortices.

All in all, this is an excellent volume well worth reading whether you are a visual scientist, ocular motorist or clinician with an interest in clinical neuro-ophthalmology.

CHRISTOPHER KENNARD

The Motor Cortex. By Hiroshi Asanuma. 1989. Pp. 189. New York: Raven Press. Price $81.50.

Ever since the early days of Ferrier and of Fritsch and Hitzig, who first demonstrated a truly 'motor' function of the cerebral cortex, there has been a continuing interest in the functions of the motor cortex, because of its unique position in the hierarchy of voluntary motor control. Modern clinical and scientific method has cast the motor cortex as the chief executive of the motor system. In recent years there have been great improvements in our understanding of how it transfers its command to the skeletomuscular apparatus. Central to this understanding is the precise connectivity of the corticospinal linkage from cortex to cord. The organization of this system is telling us more and more about the likely form and structure of the command. Much work has been devoted to the question of which functions are represented in the motor cortex, and recent studies suggest that the motor cortex does not only serve to execute the programs prepared in other structures, but may itself take part in these important functions.

In this book Hiroshi Asanuma presents his own special view of the motor cortex. In the foreword he states that his survey will draw largely upon the results of research obtained in studies from his own laboratory. His other main purpose is to present a chronological account of the ideas and discoveries that have formed the basis of our current understanding of motor cortex function. In my view this book fails on two counts: first, a historical account does not necessarily mean that developments can only be described in strict order of publication date. The author makes little attempt to gather developments together into some sort of logical progression. For example, there are 3 chapters on the anatomy of the motor cortex, dispersed at different intervals throughout the book, and the same is true of the 5 separate chapters on the anatomy and function of sensory input to the motor cortex.

The second failing arises because the citation of work outside Asanuma's own laboratory is too sparse to allow this book to serve as a useful review of the motor cortex. Those references that are cited are sometimes misquoted (there is a particularly muddled description of Evarts' classic experiment in which he first dissociated the control of muscle force from control of movement direction), and the results of other studies are sometimes curiously interpreted to fit into the theoretical framework that the author has adopted. Asanuma has a strange sense of priority in thus preferring, for instance, a full-page photograph of one of Sherrington's gorillas or the description of memory formation in Planaria, but omitting, for instance, any citation of Kuypers' work on the anatomy of the motor cortex or of Georgopoulos' work on its function during reaching movements. He describes the important property of temporal facilitation at the corticomotoneuronal synapse, a property which is probably of considerable importance during the onset of movement, when large numbers of cortical neurons burst at high frequency. But on p. 98 he states that 'no further analysis of this potentiation was made', ignoring a large amount of work on this phenomenon by Shapovalov, Porter and Muir.

The major contribution of Asanuma's early work was the introduction of intracortical microstimulation (ICMS) as a means of mapping the motor cortex, and the elegant demonstration, using this technique, of the very precise correlation between the sensory input to a given region of the motor cortex (as determined by recording responses of individual neurons via a microelectrode) and the motor output produced by delivering a train of current pulses through the tip of the same electrode. This type of input-output organization is probably of great importance during skilled movement, and especially during tactile exploration.

The concept which Asanuma introduced in the late 1960s and 1970s that the motor cortex was organized into discrete columns controlling individual muscles was challenged by the finding that the axons of individual corticospinal neurons were highly collateralized within the spinal cord and made contact with several motor nuclei. These connections have since been repeatedly demonstrated to exert direct functional excitation on target motoneurons of several different muscles. This work (notably by Fetz) receives short shrift in this book and Asanuma describes this collateralization as 'random remnants of redundant connectivity'. But this connectivity has also been shown to subserve the organization of natural movements, nearly all of which, including those studied so successfully by Asanuma in recent years, involve the coordination of multiple muscles, and it has become increasingly difficult to understand how a series of cortical columns, each addressing a solitary muscle, could function during such movements.

In 1990 there is really no need to revive the 'ghost' of whether 'muscles or movements' are represented in the motor cortex: this is a largely artificial antithesis and a question that electrical stimulation alone could never answer. The aggregation within the motor cortex of groups of neurons influencing different sets of muscles, i.e., with different 'muscle fields' is largely overlooked in this book. Despite the fact that even in his own work on the monkey motor cortex he has been able to evoke thumb movements in three different directions from sites less than 750 μm apart (fig. 24), Asanuma claims that any studies which refute a simple organization of one muscle per efferent column 'obscure the basic structure of the motor cortex'. In this argument he has failed to recognize the power of averaging techniques for detecting multiple effects in different (yet functionally related) muscles. Nor is he prepared to take into account the important differences in the effects of trains of ICMS pulses, which are known to produce powerful synaptic facilitation within the cortex, and the action of single pulses which has proved a very useful means of defining the muscle fields of clusters of cortical neurons. Most of these muscle fields appear to be organized in terms of 1–3 muscles which serve as the 'focus' of the movement, combined with a wider pattern of excitatory and inhibitory effects on other muscles, which may well function to provide the essential postural support required for efficient function of the focal 'prime movers'.

The later chapters in this book deal with Asanuma's recent work on motor learning. Distinguishing deficits of learning from those of execution has always been a source of difficulty in lesion studies designed to test for the acquisition of motor skills. Nevertheless, Asanuma has accumulated an impressive amount of evidence suggesting an important role in motor learning for the sensory input from the postcentral gyrus to the motor cortex. Of particular interest is the long-term potentiation (LPT) which this input can set up in the superficial layers of area 4. This effect appears to be specific to some postcentral inputs, but not others. Interestingly, LTP was rarely seen when thalamic (VL) inputs were activated. If LTP does subserve motor learning, then these results seem to be at variance with recent studies which have emphasized the role of the motor thalamus (and its cerebellar input) in learning.

In my opinion this book is a rather unbalanced introduction for the uninitiated student. But the views expressed in it are certainly controversial and stimulating. Its publication should help to generate plenty of new ideas and experimental approaches.

ROGER LEMON

Neural Mechanisms in Disorders of Movement. Edited by A. R. Crossman and M. A. Sambrook. *Current Problems in Neurology, 9.* 1989. Pp. 455. London: John Libbey. Price £30.00.

This volume is based on an International Conference held in Manchester in April 1988 and contains 53 articles (452 pages). It comprises sections on the basal ganglia, on anatomy, pathophysiology, pathogenesis and pharmacology, and on animal models of movement disorders, as well as a clinical part covering diagnostic and therapeutic aspects including imaging and stereotactic surgery. The title of the book is misleading, since cortical and cerebellar movement disorders are not dealt with.

Since this is not a didactic work but a collection of short communications by the conference participants, the current confusion of terminology and the different concepts on neurotransmitter dysfunction become apparent. For the nonspecialized reader it is a hard task to work through the book. Many authors dive into the midst of their super-specialized contributions without making any effort to relate to other articles. Successive articles about rat and monkey basal ganglia anatomy or lesion experiments use totally different terminologies and offer no explanations or discussions on the substantial differences between species or of experimental designs. There is no attempt to evaluate or synthesize the partly controversial observations.

The book does, however, contain a number of excellent short articles about the state of the art of different aspects of basal ganglia disorders and their experimental models. It will not serve as a concise or coherent survey on basal ganglia disorders and it has little didactic impact, but it may be most valuable as a reference book for groups working close to this issue.

H.-J. FREUND

Non-Invasive Stimulation of Brain and Spinal Cord: Fundamentals and Clinical Applications. Edited by Paolo M. Rossini and Charles D. Marsden. *Neurology and Neurobiology,* Volume 41. 1988. Pp. 328. New York: Alan R. Liss. Price $96.00.

Ten years ago, Merton and Morton gave birth to an exciting field of applied neurobiology when they used transcranial electrical stimulation to study conduction in motor pathways within the human CNS.

Five years later, Barker *et al.* showed that transcranial magnetic pulses produced electrical currents within the CNS that also stimulated motor as well as other pathways. The existence of those techniques, particularly the latter which is much less uncomfortable, has resulted in many clinical and fundamental research projects. During the preceding decade, somatosensory evoked potentials proved to be useful and interesting; motor evoked potentials are now in an early phase of their development.

The cerebral cortex, peripheral nerves and roots can be stimulated quite easily using electrical or magnetic pulses applied to skin overlying them. It is more difficult to stimulate the cord from the surface, especially magnetically. Localizing the site of stimulation is rarely possible and magnetic stimuli are worse in that respect. Both forms of stimulation appear to be safe but it is early days yet. Transcranial stimulation of motor structures has raised questions which lead to research both into the detailed anatomy and physiology underlying it and into its correlation with various clinical conditions and role as a clinical neurophysiological tool. How does this stimulation work, which tracts are involved, what does it measure and how will it be useful?

This volume, which evolved from a workshop at the last (VIIIth) International Congress of Electromyography and Related Clinical Neurophysiology, contains preliminary answers to such questions. Many more studies have been published in the past 2 years but those interested in surface stimulation of the CNS would do well to begin with this volume. Highlights include a uniquely helpful chapter by Bentivoglio with details of corticospinal connections, an exposition of methodology by Rossini and Caramia, a discussion of safety aspects by Barker *et al.*, a review of clinical applications by Thompson *et al.*, Swash's chapter on disorders of pelvic floor and sphincters, the use of motor evoked potentials for monitoring during surgery by Levy and comparisons of transcranial with direct stimulation of motor cortex by Katayama *et al.* Unfortunately, Amassian and Cracco did not contribute a review of their important work in this field.

This volume has been carefully edited, nicely printed and well indexed. Each of the 24 chapters is complete within itself—fortunately there is no resemblance to the usual proceedings of meetings in which transcripts of disjointed talks masquerade as a book. I recommend this work to clinicians and scientists interested in the motor system.

ROBERT R. YOUNG

Neural Programming. Edited by Masao Ito. Taniguchi Symposia on Brain Sciences No. 12. 1989. Pp. 254. Basel: Karger. Price £60.00.

Over the past 30 years, investigators into the control of eye movements have had an astonishingly productive collaboration with mathematical modellers. Indeed, at one time it seemed a mark of scientific modesty that researchers into the control of body movements would ask advice of their more advanced colleagues in eye movements on how to formulate and test hypotheses about the control of three-dimensional limb movement. Copying the early models of eye movement mechanics and neuronal burst, ramp and integrator mechanisms, there were attempts to describe the action of muscle spindles and servo-loops in mathematical terms. Unfortunately, precise description did not increase insight into function. Indeed, so much did modelling seem to obscure the question of function rather than reveal novel insights, that Professor P. B. C. Matthews was once provoked, in a published critique, to demand of an arch-modeller, 'How much is new, how much is true, and how much is relevant?'

The contributions in this book come from the three fields of limb movement control, eye movement control and neuronal modelling. The aim, in the words of the editor, Professor M. Ito, is to stimulate the development of 'new design principles for neural programming ... through such interdisciplinary cooperation'. Unfortunately, as the contributions show, this does not yet seem to have happened. The field of limb movement control steadfastly pursues its own parallel course, while modelling and eye motor control continue their successful collaboration.

The book is the outcome of the 12th Taniguchi Symposium on Brain Sciences held in Japan last year. The four sections of the book cover motor programming in the cerebral cortex, the contribution of cerebellum, basal ganglia and thalamus to neural programming, programming in the visual system, and programming in neuronal networks. All have short but concise contributions from acknowledged world experts in the field. As usual, the articles are a mixed bag of excellent and average, some being readable and others impenetrable. In the interests of objectivity, I calculated the readability or 'fog index' for three of the contributions using the formula: fog index = (average number of words per sentence + percentage words with three syllables or more) × 0.4. The higher the fog index the more difficult the article. A clear winner was a remarkably dense chapter by Gerfen on 'The neostriatal mosaic: compartmental organisation of corticostriatal input, striato-nigral output and dopaminergic systems' with a fog index of 29. At the other end of the scale, Georgopoulos had a very clear chapter on 'The motor cortex and reaching' with a fog index of only 19. The chapter on neuronal modelling by Atkeson and Reinkensneyer scored 22. Perhaps we would all do well to recall the advice that a fog index greater that 15 usually means that an article is too difficult to understand on one reading.

Although I found the book useful in providing an overview of several different fields, it would have been greatly improved by inclusion of some account of the discussion at the meeting. With all those brains gathered together in one place, surely more happened than each author producing a review of his latest work? What did Georgopoulos think of Grossberg's discussion of vector map versus vector difference codes? Did Passingham find the modelling of any relevance to his lesion experiments in monkeys? How far can we generalize Hikosaka's model of the basal ganglia's role in the initiation of eye movements to initiation of limb movements? If the book had the answers I would recommend buying it. Unfortunately what was discussed is secret or forgotten.

JOHN C. ROTHWELL

Neurophysiology. Second edition. By R. H. S. Carpenter. 1990. Pp. 387. London: Edward Arnold. Price £17.95.

This second edition of *Neurophysiology* is one in a series on Physiological Principles of Medicine, in which each system is covered by a pair of volumes, one preclinical and one clinical. The new edition of Carpenter's *Neurophysiology* is a straightforward update of the previous edition, following a very similar pattern of approach, content and layout. Some of the rather confusing figures of the first edition have been improved, and the text has been generally brought up to date, with a particular expansion of the sections on pain, subcortical visual mechanisms and eye movements, central auditory mechanisms, and the hypothalamus.

The preface to the first edition made the point that most physiology texts tend to dwell far too much on 'mechanism' or how a system works, rather than on 'function' or what the system actually does, resulting in students being overloaded with factual detail. Carpenter's aim was thus to stress function, in the hope of avoiding the student becoming grossly overloaded with mechanistic detail. In this, at best, he could only be said to have been partially successful, even in the first edition, as the book contains virtually as much factual detail as any other text at a comparable level. As an example, the book gives a useful and understandable nonmathematical interpretation of the hypothesis for cerebellar function based on David Marr's complex theory. Surely this is an example of 'mechanism', or even hypothetical mechanism, of how the cerebellum does what it does, rather than an illustration of cerebellar 'function'. In this new edition, as stated in the preface, the amount of 'factual detail that is so greatly enjoyed by both students and examiners' has been increased still further. Perhaps this is unavoidable—after all, physiology is about how things operate, about the mechanisms, and not simply a description of 'function'. While agreeing that today's student seems to be besieged by masses of detailed information, I do not see this book as being their way to salvation.

Putting this aside, the new volume is an interesting, readable and up-to-date text on neurophysiology, aimed at the undergraduate medical or science student. Starting from the level of membrane potentials, it progresses through the usual sections on sensory and motor mechanisms to emotion, motivation, and in its final section even manages to mention Descartes, Freud and Wittgenstein. Despite this apparently wide coverage, there are some omissions. For example, referred pain receives only a passing mention, such that a student who only read Carpenter would barely know what the term means. No attempt is made to explain the mechanism. Compare this with the treatment of the cerebellum mentioned above. As seems to be standard practice, the autonomic nervous system and its central control mechanisms are left for others to describe, but it is otherwise a book which covers everything the student would want.

D. J. BRADLEY

Listening. An Introduction to the Perception of Auditory Events. By Stephen Handel. 1989. Pp. 597. London: MIT Press. Price £35.95

Stephen Handel's book *Listening* is a massive and impressive compendium of information concerning the production and perception of sound. It is extremely well written with a free-flowing style that makes it easy to read even when the subject matter is difficult.

The book is not, as the title might suggest, a manual to assist one in learning the art of listening to sounds; rather it is a combination of an introductory text on auditory perception and a reference manual of auditory experimental psychology. The subtitle of the book, 'An introduction to the perception of auditory events', is a more accurate representation of the contents, although the implication that the book will reveal how the auditory system constructs auditory events from the booming buzzing confusion of input is not, of course, realized.

The book begins with 5 engaging chapters on the production and propagation of speech sounds and musical notes. Next is a bridging chapter on the relationship between the physical world and the perceptual world, and then there are 5 authoritative chapters on the perception of music and speech sounds. Finally, there is a remarkably current reference chapter on the physiology of hearing for those who become interested in how and where the operations are performed. With a total of 600 pages, it is undoubtedly the most comprehensive book available on auditory perception and I heartily recommend it. The remainder of this review sets out the main highlights and a few lowlights with the intention of helping the reader locate the value of the former and avoid the irritation of the latter.

The book takes the form of a graduate-level text, a set of chapters on a related set of topics that go together to form a course. It would have to be a full year course but that is what it would take to cover auditory perception at this level of detail. The academic form is one of the books main strengths. When combined with the author's gift for didactic writing, it ensures that the book is cohesive despite its length and the wide variety of topics. At the same time, the academic form gives rise to some weaknesses, one of which is a tendency toward introductions that lead the reader away from, rather than towards, the intended subject matter. For example, Handel opens the first chapter with the impossible old chestnut, 'Would you rather be deaf or blind?' and then argues for blindness. It certainly commands the reader's attention, but like so many emotional appeals, it causes an immediate digression away from the science that is the purpose of the book. In cases like this, the digressive introduction seems to be motivated by the presumed need to get the attention of undergraduate readers. In other cases, a chapter introduction presents what it seems the author would like the chapter to be about even when it is clear that it cannot be. For example, Handel begins Chapter 8 with 'I have always been fascinated by the ease with which we can identify a caller over the telephone' and proceeds to introduce research on voice identification as if it were about to be explained. But voice identification is one of the thorniest areas of auditory perception and so, not surprisingly, the chapter moves immediately to attribute identification and methods for assessing perceptual similarity, both of which are more tractable but far less interesting. In summary, the reader should be forewarned that some of the introductions are digressive and/or confusing, and should be prepared to skim over them to the heart of the chapter which is almost invariably excellent.

Following each introduction, Handel presents the primary business of the chapter, a description of basic acoustic facts or basic perceptual phenomena, along with a description of the effects of varying the pertinent physical variables. These sections are masterful and as a set they would justify a book on their own. Each section is concise but complete; furthermore, they are easy to read. In Chapters 4 and 5, he describes the production of musical sounds (violin, trumpet and clarinet) and speech sounds (vowels and consonants) using the traditional source-filter approach. By consistently focusing on the spectrum of the source vibration (e.g., string and bow for the violin and vocal folds for the voice) and how that source spectrum is modified by the attached body, he not only describes the resulting sounds but also brings across the method of analysis and makes it clear how to approach new sound sources in the future. In Chapters 7 and 9, he presents delightful, compact overviews of two relatively new areas of auditory psychology, stream segregation and categorical perception. These descriptions reveal an enviable ability to weld together information gathered from different research groups using differing experimental techniques into a sensible story with a sense of purpose and direction that is often lacking in the original papers. At the same time, he does it without glossing over difficulties or conveniently selecting material so as to avoid them. Chapters 10, 11 and 12 present classic and thoroughly enjoyable descriptions of consonance, rhythm and auditory physiology.

In most of the chapters, after setting out the main effects, Handel proceeds to take one or two of the main issues and deal with them in-depth. For example, in Chapter 10, after describing tonality, the cycle of fifths and harmony, he proceeds to a detailed description of recent attempts by psychologists to measure key-distance objectively. The relationship between the traditional representation of musical structure and the psychological representation is complex, partly because the motivations underlying the two enterprises are very different. Nevertheless, he provides an effortless transition and makes the connection seem obvious. With regard to teaching, these sections are invaluable in showing how to do a literature review and present a compact summary. With regard to content, many of these in-depth sections are illuminating (Chapter 5 on speech production, Chapter 7 on stream segregation, and Chapter 11 on rhythm). Although others are less satisfactory and leave an uneasy feeling at the end (Chapter 6 on perception and physics, Chapter 8 on identification and timbre, and Chapter 9 on categorical perception), this unease may follow more from the state of the research than from Handel's presentation of it.

Although the book is more comprehensive than any other in the field, nevertheless there is one major omission and that is a proper description of pitch perception. It is particularly surprising in a book that focuses on everyday sounds because the pitch of these sounds is not explained by the simple engineering model associated with Helmholtz and the mel-scale. In that conception, we hear a pitch if and when there is a local peak in the frequency spectrum. The spectra associated with the vowels of speech and the notes of music almost invariably contain many peaks; however, these sounds usually produce only one unified pitch corresponding to the fundamental of the harmonic series in the spectrum. Furthermore, when speech or music is presented over the telephone we continue to hear the pitch of the fundamental even though the telephone system does not pass energy at those low frequencies (below 300 Hz). Handel equates pitch with physical frequency in Chapter 2.5 (The psychophysics of audition) and with fundamental frequency throughout Chapter 10 (when discussing musical notes and scales), but the conflict between the two conceptions of pitch is never raised.

In summary, I have enjoyed listening to Handel. His coordinated series of lectures has enabled me to catch up on neighbouring fields of research in a most efficient manner, and I recommend the book to everyone interested in auditory perception.

Roy Patterson

Magnetic Resonance of Myelin, Myelination, and Myelin Disorders. Edited by J. Valk and M. S. van der Knaap. 1989. Pp. 390. Heidelberg: Springer. Price DM 348.00.

It is well known that magnetic resonance imaging (MRI) is sensitive in demonstrating the wide spectrum of pathological changes which involve the cerebral white matter. In this context the present volume is a useful contribution, providing a review of the MRI findings in a large number of congenital and acquired diseases which partially or predominantly involve the white matter. It also does more than this, in providing a considerable amount of information on the clinical features, laboratory investigations, pathology (histological and chemical) and therapy of various disorders. The authors, a neurologist and neuroradiologist, also suggest a new classification of hereditary white matter disorders, which is based on the subcellular site of enzymatic defects, e.g., lysosomes, peroxisomes.

The book starts with a chapter on disease classification, and then follow a particularly useful chapter on the composition of myelin, and a much briefer one on basic principles of MRI. There is then a section on normal and abnormal patterns of myelination, after which the main body of the book is directed to the various specific disorders. The volume ends with one chapter on pattern recognition of white matter disorders by MRI, and another on magnetic resonance spectroscopy.

The text is liberally illustrated throughout with MRI examples, although there are a few gaps where no example was available at the time the text went to press, e.g., Krabbe's disease. Some of these gaps would now be filled by subsequently published studies.

In the chapter on multiple sclerosis (MS) the authors emphasize, in some detail, 4 variants: classical MS, neuromyelitis optica, concentric sclerosis and 'Schilder's disease'. Such distinctions are rarely an issue in clinical practice, and have perhaps been overemphasized. Also, it is incorrect to suggest that older lesions in MS have lower signal and newer lesions have higher signal on T_2-weighted sequences—old periventricular lesions sometimes have a very long T_2.

Overall, this is a thorough, well referenced and well illustrated volume. It will be particularly useful to paediatricians and radiologists with a neurological interest. It would be eminently suitable in libraries attached to departments of paediatrics, radiology, and neurology. A second edition might be anticipated in the not too distant future, given the rapid changes occurring in this field.

D. H. MILLER

Visualisation of Brain Functions. Wenner-Gren International Symposium Series, Volume 53. Edited by D. Ottoson and W. Rosene. 1989. Pp. 334. Basingstoke, Hants: Macmillan. No price stated.

This volume represents the proceedings of a symposium held at the Wenner-Gren Centre in Stockholm in June 1988. The symposium which was attended by many distinguished scientists, was devoted to the theme 'Visualisation of brain functions'.

The proceedings are divided into 5 main sections of fundamental brain imaging: (1) molecular and immunohistochemical approaches, (2) functional imaging of receptors, (3) in vivo exploration of brain functions, (4) magnetic resonance and (5) new trends in neuroimaging. The last category includes papers on magnetoencephalography, and optic imaging of cortical activity. The volume consists of 29 papers.

The symposium thus covered a wide range of techniques and areas of research and the individual papers vary from being a general review of established techniques at one end of the spectrum, to reports of specific techniques under development at the other. Many of the techniques are not clinically applicable. The main areas of clinical interest at present are positron emission tomography (dealt with fairly well in a number of papers) and magnetic resonance (covered less well). More comprehensive reviews of these two areas are obtainable elsewhere. Thus this volume will not have much appeal to neurologists in general. Its main use will be for neuroscientific researchers who are involved in the particular fields encompassed by the symposium.

D. H. MILLER

Memory Disorders in Clinical Practice. By Narinder Kapur. 1988. Pp. 289. Guildford, Surrey: Butterworth. Price £39.50.

In the preface of his book Narinder Kapur argues that since the publication of Ribot's 1885 monograph *Diseases of Memory*, there have remained two important gaps in the literature on organic memory disorders. First, attempts to review the research on memory disorders from the perspective of clinical pathology have been very limited. Secondly, there has not been a systematic attempt to describe the milder and relatively 'impure' memory disorders that are most frequently encountered in clinical practice because of the amount of attention that has been paid to the more severe and purer amnesic syndrome. Kapur's book does much to fill these two gaps and will be of particular use to those who regularly deal with memory-impaired patients and wish to have state-of-the-art knowledge about the neurological conditions underlying impaired memory, how to assess such impairment, the best methods of management of each condition, and some information about what memory processes have been disrupted. Unlike other recent texts on memory disorder, this volume provides useful information in its first chapter about where to obain standardized memory tests and batteries, and two appendices, the first of which gives a list of sources that can be used for preparing special purpose memory tests and the second of which lists material relevant to the remediation of memory disorders. In addition to offering these useful practical aids for those pursuing research into memory disorders, Kapur's book gives a comprehensive review of the memory pathology literature (there are 50 pages of references), which will be invaluable to anyone needing rapid access to current knowledge about a wide range of conditions.

The tone of the book is set by the first chapter, which is concerned with assessment. The first figure in this chapter is a flow chart designed as a guide for identifying aetiology from the severity and pattern of presenting memory symptoms. The intention is to highlight the relationship between particular patterns of memory deficits and aetiology rather than to suggest that aetiology should only or best be discovered by examining the memory deficits a patient shows. The remaining 9 chapters review the main conditions that have been associated with memory disorders. These are cerebrovascular disease, cerebral tumours, penetrating head injury, blunt head injury, the dementias, infectious and metabolic diseases, toxic and deficiency states, epilepsy and the ablation or disconnection of cerebral tissue. Each of these chapters has a useful and fairly detailed summary. There are many helpful and concise vignettes of less well-documented kinds of memory disorder. For example, the susceptibility of medial temporal lobe structures to damage from hypoxia is described in the chapter on infectious and metabolic diseases as is the tendency for patients with this aetiology to show relatively mild recognition impairments and very little retrograde amnesia.

The example of memory deficits associated with hypoxia also serves to illustrate my only reservation about Kapur's book. Many of the aetiological conditions associated with poor memory affect overlapping brain regions. Despite this, as Kapur notes, the degree of memory disruption associated with some conditions is greater than that associated with others. Comparisons are also made harder because the amount and kind of brain damage caused by a specific kind of pathological process varies considerably. The book would have been enhanced by a final chapter that systematically compared the severity and nature of the memory disorders caused by different pathological processes, which damage overlapping brain regions. It is unclear whether the different pathologies have somewhat distinct effects on memory because they damage different structures, damage the same structures but to different extents, or for other reasons. Although Kapur does make some useful comparisons across chapters, this issue is so complex and important that it warrants a detailed and systematic treatment. Thus, hypoxia, for example, does occasionally cause relatively selective damage to the CA1 field of the hippocampus, but in many patients the damage caused may be far more extensive. There is strong evidence that the severity of the associated memory disorder is greater when structures other than the hippocampus are implicated. Patients who have suffered a herpes simplex encephalitis, and the patient H.M., all of whom have extensive medial temporal lobe damage, have much more severely affected memory than did the hypoxic patient R.B., who had relatively selective damage to the hippocampus. It is important to decide whether this is because the former patients have worse hippocampal damage, damage to other structures (amygdala or temporal cortex), or whether the cause of the damage is the critical factor.

The above is, however, only a small caveat about a generally excellent review that successfully fills an important gap in the literature on memory disorders. The review is so comprehensive and the referencing so thorough that Kapur's book should remain an important standard for many years.

ANDREW MAYES

ANNOUNCEMENTS

European Association for Clinical Neuropharmacology

The 8th European Workshop on Clinical Neuropharmacology will be held in Groningen, The Netherlands, on September 27–29, 1990. For further details, contact Congress Office Tonne Verdonk, De Pinckart 54, 5674 CC Neunen, The Netherlands. Telephone 031-40-631152.

Good Samaritan Hospital and Medical Center

The Good Samaritan Hospital and Medical Center, Portland, Oregon, USA, will be sponsoring a workshop on Nerve Injury and Pain on November 16–17, 1990. For further information, contact Sharon Newman, Conference Coordinator, Good Samaritan Hospital and Medical Center, 1015 Northwest 22nd Avenue, Portland, Oregon 97210.

Ecuadorean Congress of Neurology

This congress, which will be organized by the Ecuadorean Society of Neurology, will be held in Quito, Ecuador, on May 7–10, 1991. The main themes will be muscle diseases, Lambert-Eaton myasthenic syndrome, peripheral neuropathy including diabetic neuropathy, and brain trauma. There will be invited international speakers. For further information, contact the Secretary, Ecuadorean Society of Neurology, PO Box 2821, Quito, Ecuador. Telephone 541881 554865.

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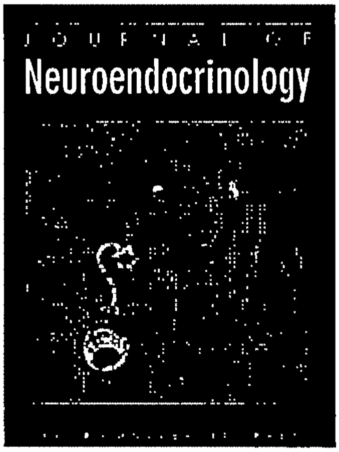

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The following documents are required for awards under each scheme:

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2. an account of the purpose of the visit;
3. the names of two referees;
4. a letter of invitation from the host department;
5. a statement of the costs with details of related applications;
6. a list of previous awards given by the Guarantors of Brain.

Four copies should be sent to Professor Alastair Compston, Honorary Secretary and Treasurer to the Guarantors of Brain, Department of Neurology, Addenbrooke's Hospital, Cambridge, CB2 2QQ (Tel. 0223 217091).

All successful applicants are expected to submit a short report of the visit on their return.

Contents continued from front cover

Mood disorders after stroke and their relation to lesion location. A CT scan study. A. House, M. Dennis, C. Warlow, K. Hawton and A. Molyneux 1113

Impaired memory for new visual forms. J. R. Hanley, N. A. Pearson and A. W. Young 1131

Movement variability and bradykinesia in Parkinson's disease. M. R. Sheridan and K. A. Flowers 1149

Perceptual and conceptual mechanisms in neglect dyslexia. Two contrasting case studies. M. Behrmann, M. Moscovitch, S. E. Black and M. Mozer 1163

Processing of local and global musical information by unilateral brain-damaged patients. I. Peretz 1185

Lyme neuroborreliosis. Peripheral nervous system manifestations. J. Halperin, B. J. Luft, D. J. Volkman and R. J. Dattwyler 1207

Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. Th. De Broucker, P. Cesaro, J. C. Willer and D. Le Bars 1223

Book reviews 1235

Announcements 1249

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